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ARMSTRONG LABORATORY

PROCEEDINGS OF THE CONFERENCE ON CHEMICAL RISK ASSESSMENT IN THE DoD: SCIENCE, POLICY, AND PRACTICE

H. J. Clewell III, Editor

MANTECH ENVIRONMENTAL TECHNOLOGY, INC.
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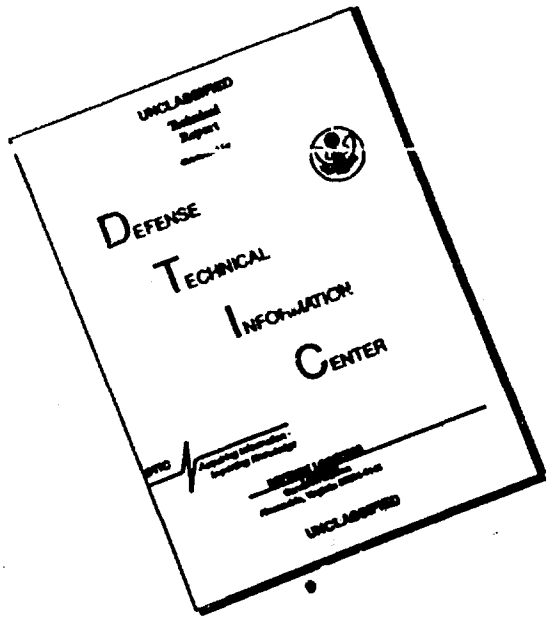

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This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

JAMES N. McDOUGAL, Lt Col, USAF, BSC
Deputy Director, Toxicology Division
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This conference was held to promote the exchange of information between those who develop risk assessment methodologies and those who perform risk assessments for the Department of Defense (DoD). The conference featured invited presentations by noted individuals in the field of risk assessment and a poster session on studies relevant to the conference theme. Sessions were held on: DoD approaches to chemical risk assessment, principles of chemical risk assessment, issues in the science and methodology of chemical risk assessment, current applications of chemical risk assessment in the military, new directions in chemical risk assessment methodologies, and issues in risk management. Special topics in chemical risk assessment highlighted the history of the three service toxicology units.

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Conference on Chemical Risk Assessment in the Department of Defense (DoD): Science, Policy, and Practice

Editor

Harvey J. Clewell, III

American Conference of Government Industrial Hygienists, Inc.
Cincinnati, Ohio

The Conference on Chemical Risk Assessment in the Department of Defense (DoD): Science, Policy, and Practice was held at the Holiday Inn Conference Center in Dayton, Ohio, from 9 through 11 April 1991. The conference was sponsored by the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory; the Toxicology Detachment, Naval Medical Research Institute; and the Army Biomedical Research and Development Laboratory, with the cooperation of the National Research Council Committee on Toxicology. Dr. Richard D. Thomas, National Research Council, National Academy of Sciences chaired the Conference.

ManTech Environmental Technology, Inc., Toxic Hazards Research Unit, coordinated the conference under Department of the Air Force Contract No. F33615-90-C-0532 (Task No. C01). Lt Col James N. McDougal served as Contract Technical Monitor for the U.S. Air Force, Armstrong Laboratory, Toxicology Division.

The technical proceedings of this conference were published by the American Conference of Governmental Industrial Hygientists, Inc., Cincinnati, Ohio (ISBN: 0-936712-90-2) in September 1992 and are reproduced herein with permission of the publisher. The technical proceedings is followed by an Appendix containing the abstracts of the posters presented at the Conference.

The opinions contained in this report and the views expressed in these papers are those of the authors and are not to be construed as official or reflecting the policy or position of the Department of Defense, its individual components, or the U.S. Government.

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V. New Directions in Chemical Risk Assessment Methodologies

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VII. Topics in Chemical Risk Assessment

Preface

The Conference on Chemical Risk Assessment in the Department of Defense (DoD): Science, Policy, and Practice was held at the Holiday Inn Conference Center in Dayton, Ohio, from 9 to 11 April 1991. The conference was sponsored by the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory; the Toxicology Detachment, Naval Medical Research Institute; and the Army Biomedical Research and Development Laboratory, with the cooperation of the National Research Council Committee on Toxicology. The conference was coordinated by ManTech Environmental Technology, Inc., and was attended by over 250 representatives of government, industry, and academia in the field of chemical risk assessment.

The goals of the Conference were to promote exchange of information between those who develop risk assessment methodologies and those who perform risk assessment for the DoD. Specifically, the goals were

- to acquaint DoD practitioners with the state of the art in chemical risk assessment methodology for occupational, environmental, and emergency planning applications.
- to acquaint those who perform chemical risk assessment with the requirements and problems specific to the DoD.
- to identify research priorities to improve the application of chemical risk assessment methods to DoD scenarios.

The Conference featured invited presentations by noted individuals in the field of risk assessment and a poster session on studies relevant to the Conference theme. A special evening session highlighted the history of the three service toxicology units. Sessions were held on:

- DoD Approaches to Chemical Risk Assessment
- Principles of Chemical Risk Assessment
- Issues in the Science and Methodology of Chemical Risk Assessment
- Current Applications of Chemical Risk Assessment in the Military
- New Directions in Chemical Risk Assessment Methodologies
- Issues in Risk Management

The papers in this volume span this wide range of topics and will hopefully provide a useful resource for individuals involved in the relatively new and rapidly growing discipline of chemical risk assessment.

I am grateful for the suggestions of my many colleagues who took time to review the manuscripts that make up this proceedings. I would also like to thank JoAnne Barker, Pam Denton, and Patty Fleenor, of ManTech Environmental Technology, Inc., for their invaluable assistance in coordinating, compiling, and editing that helped to bring this proceedings to its completion.

Harvey J. Clewell, III

Introduction

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Past

In a way, chemical risk assessment is both a young discipline and an old one. As Dr. John Doull suggests in his presentation, while modern risk assessment is less than 20 years old, toxicological hazard assessment is likely to have been the second oldest profession.

Our ancient ancestors found it necessary to categorize their environment into foods, remedies and poisons, and by the time of Louis XIV, the king considered it beneficial to his own longevity to outlaw the profession of poisoner. The earliest concerns related to unintended chemical hazards were prompted by the association of chemical exposure with occupational illness, as first recorded in 1713 by Bernardino Ramazzini in his classic work, "Diseases of Workers." Commenting on the "harvest of diseases reaped by certain workers from their crafts and trades," Ramazzini describes the principle cause as:

> ". . . the harmful character of the materials that they handle, for these emit noxious vapors and very fine particles inimical to human beings and induce particular diseases. . . ."

In his studies, Ramazzini identified chemical hazards ranging from heavy metals to tobacco smoke, although with regard to the latter he was quick to add:

> "However, let no one suppose that I wish to speak ill of a plant so celebrated that it has been dignified with the title 'Queen', a plant so agreeable to all Europeans, above all in those realms where the use of tobacco is reckoned a profitable source of revenue."

In spite of occasional episodes of "killer smog" (the most famous in December 1952 in London, England, caused over 3000 deaths), it probably wasn't until 1962, with the publication of Rachel Carson's *Silent Spring*, that the notion of hazardous chemicals as a threat to the environment, the food chain, and the individual became fixed in the minds of the public. From there it was a rapid downhill spiral to chemophobia best characterized by a succession of chemical names: DDT, saccharin, FD&C Red No. 2, cyclamates, nitrites, asbestos, ethylene dibromide, and Alar™.

The birth of modern quantitative risk assessment can be dated back to a 1973 U.S. Food and Drug Asministration (FDA) regulatory document, "Compounds Used in Food-Producing Animals" (Fed. Reg. 38:19226, 1973). This document specified the required sensitivity of methods for measuring trace levels of carcinogens in meat products on the basis of the "maximum exposure resulting in a minimal probability of risk to an individual (e.g., 1/100,000,000)...." However, most would consider the Supreme Court decision on benzene as the death knell for qualitative safety assessment. Referring to OSHA's responsibility to protect workers from significant risk, the Court stated:

> "It is the Agency's responsibility to determine in the first instance what it considers to be a "significant" risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk could clearly not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it." (I.U.D. v. A.P.I., 448 U.S. at 655)

Following widespread criticism of several safety decisions made by health regulatory agencies, Congress commissioned a report by the National Academy of Science. The resulting document, "Risk Assessment in the Federal Government: Managing the Process," laid the formal foundations for modern chemical risk assessment.

The evolution of chemical risk assessment in the military has paralleled progress in the general community. From an early focus on occupational health effects in munitions plants, the Army program has expanded to include evaluation of a wide range of chemical safety concerns: fungicides, flame retardants, fuels, smokes, insecticides, repellents, and even cosmetics. In response to the growing pubic concern for environmental degradation, the Army has also created a strong program in ecotoxicology and biomonitoring to support the activities of the Corps of Engineers.

Our country's entry into the "space race" stimulated

interest in the health effects of continuous exposures to space-cabin environments. In response to this concern, the Air Force developed the unique exposure systems now known as the Thomas Domes to conduct long-term, continuous exposures of test animals to potential space-cabin contaminants. The Navy, prompted in part by a similar interest in long-term continuous exposures (for application to submarine environments), colocated their toxicology unit with the Air Force's to take advantage of the unique facilities. As the country's focus changed from space to the environment in the 1970's, these same facilities were used to assess the hazards associated with a variety of Air Force and Navy propellants, fuels, and fluids.

The focus of these DoD efforts was essentially observational — looking for acute or chronic pathological changes after the exposure of laboratory animals, often in large numbers. Despite the accumulation of volumes of animal data, there was growing dissatisfaction of its usefulness due to the perceived difficulty of interpreting the significance of the animal results for humans. This did not represent a deficiency in the DoD programs, but rather reflected the limited state of the art of chemical hazard assessment at that time. The most enduring challenge of the toxicologist is the extrapolation of animal toxicity results to predict human hazard. The inherent uncertainty in the relationship between the results of laboratory animal experiments and the actual human risk from a chemical persists to this day.

Around 1980, as a first step in the direction of developing improved methodologies for chemical risk assessment, Air Force and Navy personnel at Wright-Patterson began to investigate the use of pharmacokinetic techniques to establish the target tissue dose derived from chemical exposure. This was a significant initiative toward a more quantitative approach for interpreting long-term animal toxicology experiments. The change from a purely observational approach to an approach that combines the traditional studies with quantitative modeling of the animal/chemical system has developed slowly, but the new methodology is now fundamental to the Air Force and Navy approaches to chemical hazard assessment. During the same period, the Army has made significant strides forward in developing useful, new animal models for human and environmental risk assessment. In particular, they have played a major role in the development of the medaka fish both as a potential animal model for carcinogenic bioassays and as a biomonitor for effluent safety assessment.

Present

Chemical risk assessment is a complex process. First a hazard assessment for a given chemical must be performed, usually by extrapolating the results of animal toxicology studies. This human hazard assessment must then be combined with an estimate of the potential exposure of individuals to the chemical or material in the specific situation of concern; this is termed the exposure assessment. Combining the hazard assessment for the chemical with the exposure estimate for the situation produces an overall risk assessment. Considering this estimated risk together with other costs, as well as potential benefits, to select the most acceptable alternative for a specific scenario is termed risk management. Each step in this process is fraught with uncertainty. As a result, the regulatory agencies, both state and federal, have generally employed an extremely conservative approach, with multiple safe-sided assumptions or safety factors. In recent years, however, there has been growing recognition that extremely conservative risk estimates may not be acceptable. Particularly in the case of carcinogenic risk assessment, a more realistic approach is needed which would attempt to provide a more accurate estimate of the hazard together with an estimate of the level of uncertainty involved.

Carcinogenic risk assessment differs from almost all other forms of toxicological risk assessment because of two key assumptions that are made. The first assumption is that there is no threshold for the effect of a carcinogen. For other forms of toxicity the assumption is made that there is a level of exposure — the threshold — below which the toxic effect will not be produced. For carcinogenicity the assumption is made that no level of exposure, no matter how small, is without potential for harm. The second assumption is that for carcinogens the dose-response relationship becomes linear at low doses. Taken together with the preference for conservative estimates, these two assumptions cause the action levels for carcinogens (usually expressed as the concentration associated with a certain increased lifetime risk of cancer) to be much lower than the action levels for chemicals producing other toxicities (usually expressed as a threshold concentration below which no harm is expected).

The pressures toward a more realistic risk assessment for carcinogens are twofold. First, in many cases the principal use of quantitative risk assessments is for performing relative risk assessments — that is, comparing the risk from two or more different chemicals. Examples include setting priorities for clean-up of environmental contaminants and selecting a chemical for an operation in which none of the candidate chemicals are completely free of hazard. While such comparisons can currently be made for most forms of toxicity, the current quantitative risk assessment methods for carcinogens ignore differences in the mechanism of action of different chemicals, and the heroic measures taken to assure safe-sided estimates result in quantitative estimates of potency which are essentially useless for comparative purposes. Second, these conservative estimates of carcinogenic potency have often led to exposure guidelines which are unachievable, unmeasurable, or operationally unrealistic. The significant monetary and operational costs associated with some of these very conservative estimates demand careful scrutiny of their reliability.

The difficulty, of course, is that the deficiencies in the current, extremely conservative risk assessment approach do not provide a justification for simply reducing current risk estimates. There has to be a scientific basis for obtaining more accurate estimates so that the new estimates can be defended and so that the assumptions and uncertainties involved in the process can be documented.

Future

For nearly a decade the military services have stepped beyond the bounds of traditional toxicology to develop more accurate, useful, and scientifically sound estimates of chemical hazard. Chemical risk assessment research in the future will undoubtedly be characterized by continued emphasis on computer modeling techniques as well as by an increased reliance on *in vitro* cell culture techniques. The result will not only be greater accuracy of chemical risk assessments, but also significantly improved timeliness for rapid screening of candidate materials being considered for emerging weapons systems.

Together with limited whole-animal studies, these techniques form a tiered approach which will provide the basis for useful risk assessments - risk assessments which provide a realistic evaluation of the chemical hazards associated with an operation so that alternatives can be considered on the basis of chemical hazard information in the same way that current trade-off studies can consider performance and cost information.

DoD Approaches to Chemical Risk Assessment

Chemical Risk Assessment — The Navy Occupational Approach

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In order for the Department of the Navy to withstand tests of its ability to manage occupational hazards, the essentials of risk assessment and risk management have been practiced for some time. A recent literature review indicates numerous citations dating from 1925 to the present.

Key documents pertinent to risk assessments are OPNAV INST 4110.2, "Hazardous material control and management," and BUMED INST 6270.8, "Procedures for obtaining health hazard assessments pertaining to operational use of hazardous materials." Like others, we believe that the actual steps of risk assessment are 1) the characterization of the exposure of a risk group, 2) evaluation of experimental studies, 3) calculation of risks and cases, and 4) calculation of an acceptable concentration or other end point.

While elements of risk assessments as evidenced by the historical development of our Navy programs are not new, our finished risk assessment strategies have yet to be developed. We are still primarily involved with the first step of characterizing exposures of our risk groups.

We possess significant strengths in terms of the Navy System Safety Program, which is mandated by OPNAV INST 5100.24A of October 3, 1986. Although the language of this instruction does not specifically identify risk assessment, system safety strategies are useful in the development of probable exposure scenarios.

Naval decision-making is often a form of risk assessment. Our challenge is that of applying scientific methodologies, such as those described in this conference, with time-honored risk assessment strategies learned at sea and in the field.

Introduction

In order for the Department of the Navy to withstand tests of its ability to manage occupational hazards, the essentials of risk assessment and risk management have been practiced for some time. A wide range of activites afloat and ashore require occupational and environmental health and safety support. A recent literature review indicates numerous citations dating from 1925.

In an era of increasing budgetary concern, it is often difficult to justify the Navy occupational and environmental health and safety programs. An understanding of risk assessments by managers may provide important insights into effective allocation of resources and foster sound decisions on control measures which act to minimize risks.[1]

History

This is by no means an encompassing review of all Navy efforts in the area of risk assessment pertinent to occupational and environmental health and safety. These are simply illustrations of the dedicated efforts of countless men and women who have devoted their professional activities to the protection of Navy and Marine Corps personnel.

1920s

The history of Navy industrial hygiene and occupational medicine dates from 1922 when efforts began to protect civil servants in Navy shipyards. In 1925, the Philadelphia naval shipyard conducted a survey of lead poisoning and recommended control strategies. The modified Burrell gas mask was recommended as protection against inhalation of lead fumes from shipbreaking World War I dreadnoughts.

The Philadelphia yard was the scene of additional efforts to prevent plumbism.[2] Sixty-two years later, Navy Lieutenant Lindsay Booher's paper on "Lead Exposure in a Ship Overhaul Facility During Paint Removal" would appear.[3]

1940s

World War II saw broad occupational health programs including preemployment examinations, injury care, medical surveillance, and industrial hygiene field surveys. The organization of medical services corresponded to the 12 naval districts. Emphasis was placed on conservation of manpower, with industrial hygiene and safety still in their infancy.[4] Unfortunately, by 1946, industrial health activities were demobilized.[5]

The shipyards were the consistent focus of the Navy's efforts. Through professional associations and publications, we have always benefited from the efforts of private shipyard industrial hygienists. In 1945, F.J. Viles studied the volume of welding fumes produced during arc welding operations and devised alternatives in terms of local and general exhaust ventilation.[6]

In 1943, Voegtlin and Watts[7] documented their largely unsuccessful treatment of service members who had accidentally ingested methyl alcohol. It is somewhat ironic that a similar alcohol ingestion incident occurred during Operation

Desert Storm. Today, we would call this area of endeavor clinical toxicology, but it is nonetheless part of the legacy of Navy medicine.

Critical mistakes have occurred in the assessment of risk. A report involving chest X-ray and microscopic analysis with respect to asbestos dust exposures concluded that the incidence of asbestosis was low for employees with more than 20 years of exposure.[8] It is always important to understand critical differences between survey findings (which are preliminary) and true studies that reflect proper experimental design.

1950s

In the post-World War II era, demobilization contributed to the demise of industrial health activities. There is a paucity of published data from the 1950s. A 1959 publication examined the nature of occupational health and safety programs for civilian employees, noting the role of the Bureau of Employees' Compensation and the Civil Service Commission.[9]

Techniques ranging from general ventilation using axial blowers to protective clothing (impermeable suits, head coverings, goggles, and air-line respirators) were used during the 1950s. These techniques were an attempt to minimize the risks of explosion and worker exposures to methyl isobutyl ketone and diluent toluene used in spray-painting ship interior spaces.[10] Heavy emphasis was still placed on explosion potential.

Viet Nam to 1992

In the 1960s, Public Laws 658 and 1028 formed the legislative foundation for the Navy's program, which included treatment of occupational injuries and illnesses, emergency treatment of on-the-job illnesses and medical conditions, and other activities.[11] One of the precipitating factors in the development of Navy occupational safety and health programs was the highly publicized series of aircraft carrier fires of the 1960s.[12]

Special duty assignments such as diving and other special warfare skills also prompted the development of special techniques and assessments. Collison et al.[13] pioneered the development of a direct and rapid gas chromatographic procedure for the determination of carbon monoxide in blood in which the carbon monoxide normally bound to hemoglobin is released. The method was applied to Navy divers.[13] Given the recent heightened interest in bioaerosol monitoring, it is somewhat ironic that Wright et al.[14] addressed bioaerosol considerations relative to habitability and health issues as early as 1968.

The linkages between industrial hygiene and safety were crucial to the development of Navy safety and health programs in the years following passage of the Occupational Safety and Health Act in 1970. A prime example of risk assessments peculiar to the Navy can be found in the case of Otto Fuel II, a liquid propellant used for MK-46 and MK-48 torpedoes. Rivera[15] published one of the first papers regarding this propellant in *U.S. Navy Medicine*. The critical nature of submarine atmospheres has contributed to expertise in terms of 90-day exposure standards for chemicals.[16] There is no more Navy-unique area of risk assessment than this type of analysis.

Sometimes our failures have attracted as much attention as our successes. When an automated film-developing machine was incorrectly connected to a ship's drinking water lines, 544 crewmen succumbed. Symptoms included gastrointestinal disease and elevated white blood cell counts.[17] Ship design and repair continue to be two very important areas for risk assessment.

The 1980s saw a major attempt to develop a computerized system to monitor medical information and to generate lists of hazardous substances.[18] The electronic basis for Navy occupational and environmental health recordkeeping is undergoing vast changes at present. Navy authors have also played prominent roles in assessments with respect to composite fiber field studies in recent times.[19]

The preceding discussion does not encompass all occupational health efforts in the area of risk assessment; for example, there are many contributions made by the Navy Medical Research Institute (Toxicology Detachment) that will be outlined later in this volume.

Regulatory Framework

Key documents pertinent to risk assessments are OPNAV INST 4110.2, "Hazardous material control and management," and BUMED INST 6270.8, "Procedures for obtaining health hazard assessments pertaining to operational use of hazardous materials."

Planners often speak of conceptual models of activities. The Navy conceptual framework for chemical risk assessments is built around a medical model. This basically means that we are sensitive to certain past errors that have led to overexposure and have resulted in disease. Moving beyond the assessment of risk, we have devised systems of analysis and remediation that seek to extend coverage to related substances and to similar exposure scenarios.

As an occupational health team, we work with safety professionals and managers, health-care providers, and individuals specifically trained in occupational health, including physicians, nurses, industrial hygienists, and others. Although it might seem that a highly organized scheme would work best for risk assessment, it is also true that diversity of interests leads to a desirable synthesis.

An examination of federal legislation and regulation regarding toxic substances will reveal that early efforts directed at limiting toxic releases or concentrations in media have moved toward a more thorough examination of a material's characteristics before its use. Since 1973, federal

health and safety statutes have adopted a general safety standard of "unreasonable risk" (e.g., Consumer Product Safety Act of 1973, the Federal Environmental Pesticide Control Act of 1973, and the Toxic Substances Control Act of 1976).

While we to date have not adopted "acceptable lifetime risk" figures, the Navy has followed this general pattern by moving toward controls related to the introduction and dissemination of hazardous materials.

We are students and observers of this conference and other forums for dissemination of information concerning the "acceptable lifetime risk" issue. Although the Occupational Safety and Health Administration (OSHA) may use the criterion of 1 "cancer" death per 1000 workers (1:1000) as an acceptable lifetime risk, others agencies differ. The Nuclear Regulatory Commission (NRC) opts for the ratio of 1:400 for occupational exposures, whereas the Food and Drug Administration (FDA) has interpreted court decisions to mean that a lifetime risk of 1:1,000,00 is a *de minimis* level of cancer risk (e.g., insignificant and therefore acceptable). The Navy precedent is probably based on radiation exposures where we closely followed the NRC's recommendations.

We must remember, however, that individuals may be exposed to a mixture of many substances both on the job and away from the work site. Thus, the issue is one of assessing integrated exposures. Modern techniques of biological monitoring and medical surveillance must be coupled with traditional air sampling methodologies.

The Navy has developed procedures for obtaining health hazard assessments pertaining to operational use of hazardous materials (BUMED INST 6270.8 of June 6, 1990). This instruction has the trivalent goal of 1) minimizing health hazards posed by materials or systems under development, 2) establishing formal procedures for obtaining additional toxicological information for those materials, and 3) assigning responsibilities within the Navy Medical Department for performing risk assessments.

By viewing research and development in life sciences as integral to all other research activities, BUMED INST 6270.8 attempts to ensure that risk assessments are performed early in the process. Not only is there a question concerning new materials, but the assessment process must extend to new uses of existing materials.

One of the key elements of OPNAV INST 4110.2 is the use of the term "life-cycle material and equipment requirement." With this term is a realization that the problems we encounter continue through our use and disposal (e.g., recycling) of substances.

Navy Risk Assessments

Like others, we believe that the actual steps of risk assessment are 1) the characterization of the exposure of a risk group, 2) evaluation of experimental studies, 3) calculation of risks and cases, and 4) calculation of an acceptable concentration.[20]

We similarly recognize the classification of the risk assessment process into four broad components: hazard identification, dose–response assessment, exposure assessment, and risk characterization.[21]

Although elements of risk assessments are not new, as evidenced by the historical development of our Navy programs, our finished risk assessment strategies have yet to be fully developed. We are still primarily involved in the first of four steps; i.e., characterizing exposures of our risk groups. As always, this means consideration of the human focus of the exposure, the concentration of exposure, the route of exposure, the duration of exposure, and the nature of exposure to other toxic materials that may be concurrently released.

Intense regulatory pressures and workers' compensation claims have combined to narrow our interest primarily to occupational issues. We are in the process of broadening these techniques to include other environmental concerns. Although we attempt to describe exposures to particular individuals, we still suffer information shortfalls in terms of inferential means of applying these results to other individuals (whose work patterns may differ).

Characterization of the Exposure of a Risk Group

One of the most useful techniques is the preliminary description of a possible exposure scenario. This usually involves asking a series of questions as to the nature of the release (e.g., when, where, and how the release may occur; what is in its vicinity; and what is known about the amounts and characteristics of the released agent). Remembering that this represents a hypothetical scenario, some means of organizing these factors is necessary.

One very useful way to organize events is to use an event-tree or other system safety device. The U.S. Navy has significant strengths in terms of the Navy System Safety Program, as mandated by OPNAV INST 5100.24G. Although the language of this instruction does not specifically identify risk assessment, the instruction is specific in commanders' requirements that their subordinates must "establish procedures to ensure timely follow-up to correct identified hazards, and document with proper justification management decisions to accept risks associated with identified hazards."

Evaluation of Human and Animal Studies

Other papers in this volume will outline the qualitative and quantitative evaluation of human and animal studies, which involves weighing many aspects of the respective experiments. The calculation of risks and cases for nonthreshold and threshold toxicants follows this step.

Much of this work is assigned to the Toxicology Detachment. The mission statement of the Navy Medical Research

Institute (NAVMEDRSCHINSTITUTE INST 5450.1D of November 26, 1990) charges this detachment to formulate occupational and environmental health hazard evaluations and risk assessments, including appropriate personnel exposure limits. It also charges the Toxicology Detachment to develop and maintain a cadre of Naval personnel skilled in the disciplines of toxicology, health hazard evaluations, and risk assessment.

Assigning Acceptable Concentrations

Historically, we have relied upon OSHA's Permissible Exposure Limits or the Threshold Limit Values and Biological Exposure Indices from the American Conference of Governmental Industrial Hygienists for the interpretation of occupational exposures. It is becoming more incumbent upon us to derive acceptable concentrations, not only for workroom air but also for other media and environments. As it becomes more difficult to complete this task, we are made aware of the presence of particularly susceptible individuals in the workplace for whom such standards may be misleading.

Although the Department of the Navy is not a regulatory agency, we are affected in our thinking by confusion concerning the use of conservative, realistic, and worst-case exposure scenarios. Regulatory agencies, most notably the U.S. Environmental Protection Agency, have been affected by Executive Orders 12291 and 12498, which reflect the Office of Management and Budget's concern over worst-case exposure scenarios. Numerous cases exist in which there is difficulty in assigning the scenario conditions.

Lessons Learned from Operation Desert Storm

Chemical and Biological Weapons Defense

Chemical and biological agents may be of the ordinary type or they may be warfare specific. Before and during Operation Desert Storm (ODS), efforts were focussed on many elements of risk assessment relative to chemical and biological weapons. Ironically, while use of these instruments of human misery was curtailed, the Iraqis set hundreds of oil wells on fire and released million-gallon quantities of crude oil into the Persian Gulf.

In our assessment of military risks pertinent to chemical agents, we must now acknowledge the combined effects of warfare agents plus petroleum and/or warfare agents plus industrial chemicals. We must address the purposeful use of industrial chemicals for lethal purposes. Critical issues exist with respect to monitoring and decontaminating chemical warfare agents when industrial pollutants are present.

One serious challenge in developing a conceptual framework for protection from or neutralization of biological and chemical agents is that it is difficult to envision the purposeful use of toxic substances. Workers are infrequently exposed to tiny, almost immeasurable concentrations; in contrast, enormous concentrations of chemical substances may exist on a battlefield and extend to civilian communities.

The use of chemical and biological weapons is not an issue for only military personnel. These weapons are prohibited because they do not discriminate between military and civilian populations. If unleashed, these agents will have significant effects, beginning with the very young, the very old, and the most infirm individuals, all of whom are most susceptible to toxic substances.[22]

Oil Smoke Toxicity Issues

As clouds of dense smoke rose from the burning oil fields of Kuwait, data concerning the nature of exposures to United States personnel became critical. It was necessary to record and archive these transient exposure conditions.

Simple monitoring of combustion-product pollutants was conducted, along with evaluation of fire safety procedures. Using a team skilled in occupational and environmental health and safety, multi-agency monitoring has begun to address exposures to crude oil, volatile hydrocarbons, sulfur-containing compounds such as hydrogen sulfide, combustion products, and other agents and stressors.

Exposure monitoring was intended to form the basis for the design of epidemiologic studies. When critical exposures are identified, we will seek to identify both exposed and unexposed groups. From a health effects standpoint, we wish to examine the spectrum that begins with exposure and possibly extends through the stages of biochemical and histopathological changes, organ system dysfunction, and organismal disability.

Future Concerns

Concern obviously exists because of the ecotoxicological hazards stemming from the oil, its constituents, and its combustion products. Operation Desert Storm contains important lessons related to occupational and environmental health. The importance of these lessons is underscored by operational issues that require detailed assessment of risks and hazards.

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U.S. Army Approach to Environmental Risk Assessment

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The following is the abstract of the presentation by Mr. Thies. His paper is not available for publication at this time.

The U.S. Army began the Installation Restoration Program in 1972. Currently, the Health Risk Assessment (HRA) documentation is prepared by contractors during the Remedial Investigation/Feasibility Study (RI/FS). Although members of the Army Medical Department have informally reviewed the HRA documents since the mid-1980s, the U.S. Army Environmental Hygiene Agency (USAEHA) was formally tasked to perform the technical review in 1989.

USAEHA uses a matrix of environmental scientists, engineers, toxicologists, and physicians to provide technical review of all documents involving HRA from the initial Scope of Work in the RI/FS process through the final review of the Record of Decision. In addition, USAEHA provides limited in-house field data collection and HRA documentation preparation, and coordinates the Army involvement with the Agency for Toxic Substances and Disease Registry.

To date, USAEHA has reviewed over 300 documents, prepared 5 HRAs, and saved the U.S. Army over $20 million by correcting major flaws with contractor-provided documents.

Risk Assessment/Risk Management for Emergency Response Operations

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A basic approach to risk assessment/risk management applied to operational and emergency response scenarios is discussed. Examples highlighting problems and successes in implementing the model are also presented. Applications vary from conditions where the hazardous material of interest is an Air Force unique material and involves a limited Air Force population at risk, to conditions where potential exposures involve the public. Also discussed is Air Force participation in the risk assessment/risk management process for hazardous materials that are not unique to the Air Force. A formal policy framework for implementing the risk assessment/risk management model to ensure Air Force employees and the public are protected to an acceptable risk level is proposed.

Introduction

The assessment and management of risks associated with the use of new or existing hazardous materials is an important aspect of weapon system support. The following discusses a risk assessment/risk management (RA/RM) model applied to operational and emergency response scenarios. Examples are presented to demonstrate the application of the model to Air Force operations.

Operational RA/RM Model

Risk assessment is the process of determining the exposure level that will protect the affected population from aspecified risk of developing disease. The basic RA/RM model shown in Figure 1 depicts risk assessment developed from both a hazard assessment and an exposure assessment. It is important to note these are dependent assessments. Risk management is the process of considering the risks and implementing the risk assessment in the operation.

Hazard Assessment

Within the Air Force, hazard assessment can be further broken down into prospective and retrospective hazard assessments. Prospective hazard assessments are performed on new or existing materials for which there are few toxicological data on which to base the assessment. Preferably, this is done at the beginning of weapon system development. To this end, the Air Force has established offices in the major weapon systems development divisions to evaluate hazardous materials prior to incorporation into the weapon system.

Ideally, these offices will identify candidate hazardous materials to the Toxicology Division of the Occupational and Environmental Health Directorate of Armstrong Laboratory, AL/OET, Wright-Patterson AFB, Ohio, for hazard assessments. The research toxicologists at AL/OET evaluate existing human and animal toxicology data and initiate research to fill the identified data gaps.

Animal exposures are performed in the Thomas Exposure Domes. AL/OET was involved in the initial development, and it continues to be a leader in the rapidly developing field of toxicokinetics. Toxicokinetics involve the identification of an animal model with a metabol-ic pathway similar to humans for the hazardous material of interest. Effects in the animal model are then scaled using toxicokinetic methods to estimate the effect in humans. This toxicokinetic method provides a more accurate hazard assessment of the hazardous material in humans than the normal inter- and intraspecies extrapolation techniques of traditional toxicology. The AL/OET also has the in-house and contract capability to perform predictive *in vitro* toxicology screens such as enzyme release, mechanism of action, and genetic testing.

Retrospective hazard assessments are performed on hazardous materials for which toxicology data already exist. The hazard assessment may be required because the hazardous material is new to the Air Force or because the Air Force is considering a new application for an existing hazardous material. Retrospective hazard assessments are performed by toxicologists and epidemiologists at the Occupational Medicine Division, Occupational and Environmental Health Directorate of Armstrong Laboratory, Brooks AFB, Texas (AL/OEM). They evaluate existing toxicology and epidemiology data and exposure guidelines to perform the hazard assessment. Significant toxicology data gaps are referred to the Toxicology Division. Often this review will directly result in the risk assessment based upon exposure guidelines (risk assessments) for similar materials. An example of this alternative is the risk assessment for JP-4 jet fuel based upon published risk assessments for similar hydrocarbon materials.

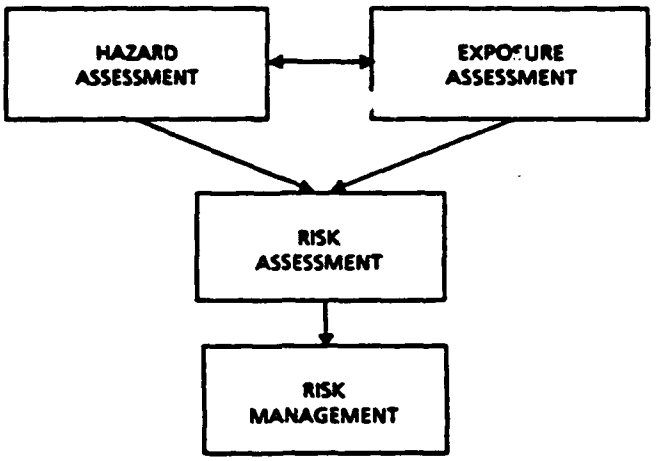

FIGURE 1. Operational RA/RM model.

Exposure Assessment

The other major component of the risk assessment is the exposure assessment which identifies the levels and routes of likely exposure to the hazardous material. Air Force exposure assessments are primarily performed by industrial hygienists assigned to the AL/OEM. The exposure assessment identifies the population at risk. It determines if exposures are limited to Air Force personnel or if there is the potential for public exposure. It also identifies the potential for exposing sensitive subgroups such as children, fertile females, asthmatics, etc. Potential public exposures of Air Force interest include emergency response operations involving the accidental release of rocket propellants.

Also key to the exposure assessment is evaluation of the analytical methods to measure exposures accurately. Methods must be available to determine airborne and surface contamination levels when appropriate. Implementing a risk assessment requiring a very low acceptable exposure is quite difficult if the exposures cannot be measured. Also important to the exposure assessment is the identification of any biological markers. Biological markers can be a very useful adjunct to other exposure monitoring.

The exposure assessment must also address the potential levels of exposure to the population at risk. This can be accomplished from actual measurements, comparison with measurements from analogous hazardous materials from similar operations, engineering calculations of evaporation, and dispersion models in the case of spills. Surface contamination must also be addressed for materials with low vapor pressure. Examples include polychlorinated biphenyls and dioxins in transformer fires and methylene dianiline associated with curing of composite materials.

Potential exposure patterns must be determined or estimated. Will the exposures occur daily as in occupational exposures or is the potential for exposure once per lifetime, as is assumed for accidental exposures? This once-per-lifetime exposure is the basis for the Committee on Toxicology (CoT) Short-Term Emergency Public Exposure Guidelines (SPEGL). In addition to frequency, duration is also a factor in determining exposure assessments. Will the exposure be relatively short as in the case of spills (the time for the cloud to pass or for evacuation to occur) or will the exposure be 8 hours per day in the occupational setting?

Risk Assessment

The hazard assessment and exposure assessment are integrated to produce the risk assessment — the acceptable exposure level. Risk assessments are usually performed by industrial hygiene or toxicology consultants. However, they may also be performed at our installations by the base bioenvironmental engineering services (BES) office. The BES personnel measure exposure and compare the results to exposure guidance for similar hazardous materials and operations to determine the risk assessment to the Air Force employees. The BES personnel may also contact an Air Force consultant from the Armstrong Laboratory for additional guidance in the risk assessment. These consultants have additional resources available and often have expertise in specific hazardous material areas.

The risk assessment can also be performed by existing outside consultant contractors. For installation restoration program (IRP) sites, health assessments are performed by the Agency for Toxic Substances and Disease Registry of the Centers for Disease Control. (Department of Defense IRP sites are similar to the civilian Superfund sites.) The more usual approach for Air Force unique hazardous materials or operations is to request the CoT to develop the risk assessment. This is especially appropriate when the potential for public exposure exists. The independent, third party review by this eminent body of scientists is extremely valuable in our efforts to both ensure and communicate our commitment to public safety.

Carcinogen Risk Assessment

The Air Force addresses risk assessments for carcinogens differently from other hazardous materials. For carcinogens, the acceptable risk appears to be in the range of one cancer case per 10,000 exposed (10^{-4}) to one cancer case per million exposed (10^{-6}). Although this is not published in the literature, the Occupational Safety and Health Administration (OSHA) usually regulates workplace exposures to carcinogens to a risk of approximately 10^{-4}. The U.S. Environmental Protection Agency (EPA), however, usually regulates carcinogens to 10^{-6}. The difference in rationale is due to the difference in the exposure assessments. OSHA assumes a healthy workforce exposed 8 hours per day, 5 days per week for a 40-year working lifetime, whereas the EPA assumes the general public is exposed 24 hours per day for a 70-year lifetime. The general public includes sensitive

populations such as children, elderly, infirm, etc.

Based upon the hazard assessment (total dose per unit time), the acceptable risk exposures are calculated for the at-risk population using a linearized, multistage model. As an example, the SPEGL for unsymmetrical dimethyl hydrazine (UDMH) (a rocket propellant) is 24 ppm for 1 hour. The hazard assessment was based upon a carcinogenic risk of 10^{-4} for Fischer 344 rats for a 2-year, continuous exposure at 0.01 ppm. The exposure assessment for a 1-hour, once-per-lifetime exposure results in the risk assessment expressed above as a SPEGL.

Noncarcinogen Risk Assessment

For noncarcinogens, the more traditional toxicology approach is used. First, the No-Observed-Adverse-Effect Level (NOAEL) or Lowest-Observed-Adverse-Effect Level (LOAEL) is determined from animal data. To this value, safety factors of tenfold for interspecies and another tenfold for intraspecies differences are added. Other factors may be added to account for *low-* verses *no-*observed adverse effect and sensitive populations.

The risk assessment for monomethyl hydrazine (MMH) (a rocket propellant) resulted in a SPEGL of 0.52 ppm for 1 hour. This was based upon dose-related hemolytic anemia with Heinz body formation in dogs chronically exposed (6 hours per day, 5 days per week for 6 months) at 0.2–5.0 ppm MMH. This is equivalent to 156 ppm for 1 hour. Applying the 100-fold safety factors for species differences and a 3-fold factor to account for the LOAEL verses the NOAEL yields the 0.52 ppm SPEGL.

Risk Management

Risk management is the implementation of the risk assessment to ensure all affected populations are protected to the underlying risk assumptions used to develop the hazard and exposure assessments. Risk management is practiced daily at Air Force installations. The BES personnel compare measured or estimated exposures levels to risk assessment information and recommend protective measures.

Managing risk may be accomplished by using safer substitute materials. When this is not possible, engineering controls are the method of choice to protect the potentially exposed population. Administrative controls can be used to minimize the period of exposure. However, this is generally limited to radiation exposures and is not used to protect against hazardous material exposures. Personal protective equipment, primarily in the form of respirators, may also be used to minimize exposures. In the case of potential public exposure, models predict the dispersion of the hazardous material and operations are halted if public exposure above the SPEGL is possible in the event of an accident. This approach is routinely used to protect the public during rocket launches.

An important aspect of risk management is risk communication. It is important that the potentially exposed population understands the risk and efforts to minimize this risk. Title III of the Superfund Amendments and Reauthorization Act (SARA) requires users and storers of hazardous materials to notify the surrounding community of the types, quantities, and hazards as well as the risk of accidental release. It also requires coordination of emergency response actions.

The OSHA Hazard Communication Standard (29 CFR 1910.1200) requires that all hazardous materials be evaluated to ensure that hazards are identified and that this information is transmitted to the worker. This is accomplished through 1) labeling and material safety data sheets that provide safety and health information on the hazardous materials, and 2) training on their hazards.

Risk Assessment Problems

Problems in risk assessment can occur when the risk assessment is not coordinated with the appropriate offices, thereby failing to consider all aspects of the risk. Problems in risk management can occur when too much emphasis is placed on the operational considerations at the expense of the health aspects of the risk assessment.

Problems can affect Air Force health policy when a risk assessment is developed or concurs with an exposure guideline without the approval of the Air Force Surgeon General. This may establish an Air Force standard, which is the authority of the Air Force Surgeon General. The risk assessment can also affect mission operations. For example, a recent assessment of isocyanate painting operations resulted in a decision by the operators to eliminate polyurethane paints on the weapon system and to search for a suitable substitute. The risk assessment was not coordinated and may have overestimated the hazard.

The Air Force has the ability to perform top-quality risk assessments. However, consultants developing these risk assessments may not realize the overall Air Force implications of these assessments. Problems associated with the risk assessments developed within the Air Force are primarily a result of the lack of a formal policy framework for the development, coordination, and dissemination of risk assessments.

An example of a problem associated with hazard assessment occurred in the area of indoor air quality. Our consultants recommended a lower level of carbon dioxide than indicated in other consensus standards. Although the indoor air quality of the office in question may have needed improvement, the very low recommended levels resulted in 30 different bargaining issues with the local union. This almost resulted in arbitration and the associated problems.

A probable analytical error nearly resulted in an Air Force-wide alert to evaluate all family housing units for

mercury. Mercury is used in latex paints as a fungicide. An exposure assessment was initiated after a woman was diagnosed as suffering from mercury poisoning several months after her husband painted their quarters with a mercury–containing latex paint. Initial sample results indicated extremely high mercury levels 1 year after the painting. Although it is possible the woman did receive sufficient mercury to exhibit symptoms of mercury poisoning, this was probably due to the high levels present immediately after spray painting. Follow-up sampling resulted in levels within guidelines, which were probably more representative of actual conditions.

Isocyanates are an example of problems incurred in the risk assessment. The initial hazard assessments are based upon exposure to isocyanate vapors. With the reformulation of polyurethane coatings, the primary source of isocyanate exposures in the Air Force is isocyanates in aerosols, not in vapors. The analytical method to determine the exposure assessment is also questionable because it samples the vapor and is less effective in capturing the aerosol component.

Problems in Risk Management

The risk assessment levels are used in dispersion models to predict potential public exposure in the event of an accident involving rocket propellants. Problems in risk management arise in the application of these dispersion models. These models are subject to variations in predictions based upon the input assumptions, e.g., source strength, instantaneous evaporation, lack of accounting for evaporative cooling. However, rather than address these shortcomings, risk managers often request relaxation of the risk assessment exposure level. Although risk management can incorporate operational considerations, it is inappropriate to adjust a risk assessment solely to meet operational constraints.

RA/RM Model

A policy framework for the preparation, coordination, and dissemination of risk assessments should address several different exposure scenarios. These include risk assessments for Air Force unique hazardous materials with different potentially exposed populations. This population could be a small Air Force population, such as potential exposure to nitrogen tetroxide during rocket propellant loading; Air Force-wide exposures to hydrazine from F-16 aircraft operations; or potential public exposures to nitrogen tetroxide or UDMH during propellant transport over public highways or in the event of a launch accident. The policy framework must also address risk assessments for hazardous materials that are not unique to the Air Force. Examples include isocyanates and indoor air quality contaminants.

For limited exposure populations to an Air Force unique material, BES personnel can perform the risk assessment based upon published exposure guidelines. The BES personnel should send the risk assessment to the user and forward a copy to the major command for review. A recommended approach is verbal prereview with the major command and a written follow-up.

If the risk assessment is beyond the base BES capabilities, the base can forward the request to an Air Force industrial hygiene or toxicology consultant at AL/OET or AL/OEM. These consultants complete the risk assessment and send it to the requestor with a copy to the Air Force Surgeon General's office. If the risk assessment is potentially controversial, either due to the material or the population exposed, the risk assessment should be forwarded for review prior to release.

If the risk assessment involves potential Air Force-wide exposures, the Air Force Surgeon General's office should oversee the development of the risk assessment using in-house resources (AL/OEM or AL/OET). This risk assessment should be reviewed by the Committee on Toxicology. This independent, third party review provides valuable credibility. An example of this approach is the risk assessment for chlorotrifluoroethylene, a new hydraulic fluid scheduled for use in advanced aircraft.

Risk assessments for materials where there is a possibility for public exposure or public concern should follow the general procedure for Air Force-wide exposures. However, additional cooperation with outside agencies, such as EPA and OSHA and possibly manufacturers, should be pursued where applicable. Examples include the routing risk assessment for nitrogen tetroxide, which involved cooperation with the Department of Transportation and the manufacturer. An ongoing risk assessment involves the identification of substitutes for Halons. The Air Force is currently cooperating with the EPA and manufacturers to perform the risk assessments for potential substitutes. Again, this risk assessment should be reviewed by the Committee on Toxicology.

Another area of risk assessments includes materials that the Air Force uses but which are not unique to the Air Force. The Air Force should participate in the risk assessment process to share our experience and data and to ensure that Air Force operational conditions are considered. Ways in which the Air Force has and will continue to participate include providing testimony at OSHA hearings, such as for methylene dianiline; reviewing National Institute for Occupational Safety and Health draft publications and providing access to our facilities during standards development; working with EPA on the toxicokinetic model now used for methylene chloride risk assessments; and participating on many American Society for Testing and Materials committees.

Summary

In summary, risk assessment consists of two interrelated components — hazard assessment and exposure assessment. The hazard assessment defines the potential for the material

to cause illness or injury to an exposed population. The exposure assessment defines the population potentially exposed, the routes and levels of exposure, and the probable frequency and duration of exposure. Risk management is then the implementation of the risk assessment to ensure potentially exposed populations are protected to the level of risk determined from the risk assessment.

A policy framework such as that outlined needs to be followed to ensure consistent development and implementation of risk assessments within the Air Force. This will ensure that risk assessments properly reflect the policies of the Office of the Air Force Surgeon General.

Four Decades of Scientific Service: The Committee on Toxicology

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Since 1947, the National Research Council's Committee on Toxicology has provided military and civilian agencies with scientific information and expert advice on difficult issues involving toxicology and the health effects of hazardous substances. In doing so, the Committee on Toxicology has made important contributions to the field of toxicology and to occupational safety and national security.

The National Research Council's Committee on Toxicology has expertise in toxicology, chemistry, industrial hygiene, epidemiology, biochemistry, occupational health, pharmacology, physiology, pathology, and risk assessment. The Committee's specific responsibilities to its sponsoring agencies (primarily the Department of Defense) include responding to questions of broad scientific policy; making interim recommendations on allowable concentrations of air contaminants for emergency and continuous exposure; providing scientific and technical information on materials and equipment that are used or proposed for use by military and civilian agencies; organizing workshops and seminars to disseminate information and develop scientific consensus; recommending toxicologic investigations or other scientific research; recommending the elimination of redundant toxicologic research; and providing advice on and, if necessary, participating in field studies conducted by a sponsor.

Over the years, the Committee on Toxicology has recommended emergency exposure guidance levels and continuous exposure guidance levels for hundreds of substances used (or encountered) by Department of Defense personnel. In making such recommendations, the Committee performs risk assessments, especially for carcinogenic substances. The criteria and methods for calculating carcinogenic risk from low levels of long-term exposures to high-level short-term exposures (1 to 24 hr) or for continuous exposure for up to 90 days (submarine exposure scenario) have been published. Several workshops have also been organized by the Committee to develop methodology for conducting risk assessments for mutagens, developmental and reproductive toxicants, and carcinogenic mixtures. Thus, the Committee on Toxicology has been at the forefront of the development of risk assessment methodology for the protection of health and for the regulation of toxic chemicals.

Introduction

The Committee on Toxicology (COT), part of the Board on Environmental Studies and Toxicology (BEST) of the National Research Council's Commission on Life Sciences, has provided military and civilian agencies with scientific information and expert advice on difficult issues involving toxicology and the health effects of hazardous substances since 1947. In doing so, COT has made important contributions to the field of toxicology, and to occupational safety and national security.

Today, COT's members continue to include some of the nation's leading experts in toxicology, chemistry, industrial hygiene, epidemiology, biochemistry, occupational health, pharmacology, physiology, risk assessment, and pathology.

The Committee assists the government in three ways:

1. As a source of expert advice in identifying health risks and in developing acceptable exposure levels.
2. As a convener of workshops and seminars to disseminate information and develop scientific consensus.
3. As a source of scientific and technical information on materials and equipment that are used or proposed for use by military and civilian agencies.

This paper will highlight some of the Committee's work over its four decades of service and will describe its current activities showing their range and diversity.

Background

The National Academy of Sciences (NAS) was chartered by the U.S. Congress in 1863 as a private, independent body dedicated to furthering science and technology and advising the federal government on request. NAS and its associated organizations, the National Academy of Engineering, the Institute of Medicine, and the National Research Council (NRC), constitute one of the most important, independent, expert advisory mechanisms for the formation of science and technology policy in the United States and, perhaps, in the world. NRC is the working arm of NAS and the National Academy of Engineering, carrying out most of the studies done in their names. NRC prepares and distributes about 200

reports each year on matters of national, scientific, and technical importance.

Most of the studies on which the reports are based are carried out by committees, panels, and working groups (about 1000 throughout the NRC in a typical year), consisting of scientific, engineering, and medical experts. The NRC reports are readily available to government agencies, Congress, the private sector, the academic community, the press, and the general public.

History

The Committee on Toxicology is one of the oldest standing committees of NRC. Organized in 1947, COT was originally intended to be a domestic counterpart of the Commission de Toxicologie of the International Union of Pure and Applied Chemistry and to represent the U.S. professions of toxicology and industrial hygiene in international affairs. However, it was quickly recognized that there were many important domestic needs for its services, especially in the armed forces, and federal agencies began to request its advice.

Missions

The missions of COT are to provide advice to its sponsoring agencies (primarily the U.S. Army, U.S. Navy, U.S. Air Force, and National Aeronautics and Space Administration [NASA]) on toxicologic matters; to serve as an information clearinghouse; to identify information gaps; and to recommend research that can help to solve its sponsors' toxicologic problems. The specific responsibilities of COT to its sponsoring agencies include the following:

- Responding to questions of broad scientific policy.
- Making interim recommendations on allowable concentrations of contaminants for emergency and continuous exposure.
- Recommending the performance of toxicologic and other scientific research or the elimination of unnecessary research.
- Providing advice on field studies conducted by a sponsor and, upon request, assisting in the interpretation of the results of the studies.

The reports produced by COT, like all NRC reports, contain advisory information and recommendations; they do not present standards, and they do not contain judgments regarding the acceptability of health risks.

Membership

COT is composed of approximately 20 experts who are nominated for 3-year terms. Members include national and international leaders in such fields as toxicology, chemistry, industrial hygiene, epidemiology, biochemistry, occupational health, pharmacology, physiology, risk assessment, and pathology. Members are chosen for their professional ability, judgment, and integrity. They bring to the Committee's deliberations the competence that makes for thorough examination of the problems presented. They serve without monetary compensation, responding to a sense of professional and national service. Ten of the current or past Committee members have been presidents of the Society of Toxicology, and the current roster includes members of the Institute of Medicine, the Environmental Protection Agency's Science Advisory Board, and advisers to the International Agency for Research on Cancer.

Most of the work of COT is carried out by its various subcommittees and working groups. Additional Committee members and outside consultants are called upon to join these groups when special expertise is needed for particular studies.

Studies

After more than 40 years and almost 700 studies and reports, COT's publication list has come to reflect the breadth and depth of modern toxicology and environmental health science. Three characteristics of COT's work illustrate the range and scale of its output: the number of specific materials whose toxicity and health effects it has evaluated, the breadth of toxicologic topics and concerns it has addressed, and its contributions to the methods of modern toxicology.

Substances Evaluated

During the past four decades, the COT has analyzed hundreds of potentially toxic materials to which Department of Defense (DoD) personnel are likely to be exposed in a modern, technology-intensive military establishment. A few of the materials are unique to military applications, but many others are common in a modern industrial society, particularly in the petrochemical, transportation, and electronics sectors. Still others have broad applications and can be found around the home or farm.

It would be burdensome to name all the specific chemicals involved, but the following tabulation lists many of the types of materials for which COT has provided toxicologic information and advice to its sponsors:

- Munitions — explosives, pyrotechnics (e.g., signal flares), obscurants, and chemical warfare agents and their chemical precursors.
- Fuels — fuel additives, propellants, diesel and rocket fuels, and their combustion by-products.
- Engine fluids — hydraulics, lubricants, coolants, and anticorrosion agents.
- Coatings — dyes, paint additives, varnishes, sealants, adhesives, and adhesive removers.
- Cleaners — solvents, dry-cleaning fluids, detergents, disinfectants, and sterilants.

- Biocides — pesticides (especially insecticides), herbicides (including paraquat and Agent Orange), and fungicides (e.g., for protecting leather boots).
- Toiletries — insect repellents, sunscreens and other protective creams, dandruff shampoos, and camouflage face paint.
- Food-related substances — purifying agents and contaminants in potable water systems, anticorrosion agents in food service equipment, fuels for heating rations, heat-sealed plastic wrapping for meats, and preservatives for wooden chopping blocks.
- Miscellaneous substances — duplicating fluids, heat-sensitive and electrosensitive recording papers, shrink-proofing and fire-retardant treatments for uniforms, and fire-extinguishing foams and other agents.

Advice Provided

The central focus of COT's work is the evaluation of toxicity of individual substances. However, its reports have also addressed the composition of materials and the toxicity of their components, offgasses, and pyrolysis products; differential and comparative toxicity; and major routes of exposure, including inhalation, ingestion, absorption through skin, and injection.

For many hazardous substances, the Committee has made recommendations regarding continuous exposure for up to 90 days for submarine atmospheres and possible acceptable emergency and short-term exposures. Recommendations on limits for exposures have been among COT's major contributions.

The Committee has addressed the impacts of many toxic substances, including their effects on plants, animals, and even materials, as well as their effects on human health. It has reviewed acute effects; carcinogenicity and reproductive effects; and organ-specific effects, including hepatic and renal effects, blood diseases, and damage to the central nervous system. COT has also assisted its sponsors in:

- Developing exposure recommendations and procedures for the safe handling, use, and disposal of hazardous materials.
- Proposing precautionary and protective measures for exposed personnel.
- Establishing protocols for monitoring of substances and surveillance of personnel.

On several occasions, the Committee has addressed techniques and substances for treatment and decontamination, many of which carry toxic risks.

Methods in Toxicology

The Committee on Toxicology has contributed to the development of the field of toxicology through its work on toxicologic methodology. It has also assisted its sponsors in developing their toxicologic capabilities and procedures. One of COT's early reports was *Armed Forces Review of Occupational Health Methods and Equipment*, a 1955 report of proposed techniques and instrumentation for the Army.

The Committee has helped the Coast Guard to develop classification and rating systems for hazardous materials and has helped other sponsors to develop operational and safety procedures for handling toxic materials and mixtures, including protocols for monitoring, surveillance, and testing. Assistance was provided to NASA in setting up a system of basic units for expressing concentrations of atmospheric contaminants in spacecraft. The Committee has also reviewed methods for several Air Force epidemiologic studies, including protocols for its study of the health effects of exposure to Agent Orange and its contaminants.

The Committee not only evaluates toxicity and recommends exposure guidelines but also addresses the principles on which evaluations are conducted and the criteria on which guidelines are based. For example, COT has published a number of reports designed to establish principles and procedures for evaluating the toxicity of various categories of substances, notably highway fuels (1976) and household substances (1977). It has also published the proceedings of a workshop on principles for evaluating chemicals in the environment (1974). Standards proposed by the Committee were later adopted by the Environmental Protection Agency.

The focus on methods has been especially important in COT's work on short-term emergency exposure guidelines, as demonstrated by four major reports:

- *Basis for Establishing Emergency Inhalation Exposure Limits Applicable to Military and Space Chemicals* (1964).
- *Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants (1971).*
- *Criteria for Short-Term Exposure to Air Pollutants* (1979).
- *Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents* (1986).

Selected Reports

A recent compilation of COT publications — regular reports, pamphlets, and letter reports — lists 697 documents, ranging from a few pages to some with more than 1000 pages. Several of these are described below.

Short-Term Inhalation Exposure Levels

One toxicologic issue pioneered by COT is that of acute toxicity assessment and emergency responses to short-term exposures. Early in the 1960s, COT began receiving requests for information to be used in planning responses to accidental spills of such materials as rocket propellants and other hazardous chemicals. It was asked to establish guidelines for acceptable, brief inhalation exposures to airborne chemicals, much shorter than the daily, 8-hour exposure (for 5 days/week, 50 weeks/year, for 50 years) that was contemplated by the American Conference of Governmental Industrial Hygienists (ACGIH) in recommending threshold limit values (TLVs) for industrial workers.

In 1962, COT appointed an ad hoc committee to outline the first principles for such recommendations. The resulting report, published in 1964, concerned itself with emergency occupational exposures, e.g., accidental and unpredictable exposures of 10, 30, and 60 minutes. (Some sponsoring agencies had requested that limits be considered for exposures as brief as 1 minute, but the ad hoc committee felt that such recommendations would have no validity or practical value.) The report recommended emergency exposure limits (EELs, now called emergency exposure guidance levels, EEGLs) for 11 toxic materials important to the military and space agencies. The recommended exposure levels ranged from 2 to 60 times the TLVs for the same substances. The wide range led COT to the conclusion that individual, short-term exposure limits could not be set by applying a single constant ratio to TLVs and that additional scientific knowledge must be brought to bear on a case-by-case basis in setting specific EEGLs.

The Committee on Toxicology eventually recommended EEGLs for dozens of diverse substances from carbon dioxide to sulfuric acid mist. The expertise it gained in developing these guidelines for military and space-agency sponsors was called on when COT compiled three series of major reports:

- *Guides for Short-Term Exposures of the Public to Air Pollutants* (nine volumes, sponsored by the Environmental Protection Agency, published 1971–1973).
- *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents* (three volumes, sponsored by the Department of the Army, published 1982–1985).
- *Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants* (eight volumes, sponsored by the Department of Defense, published 1982–1988).

In this series, COT recommended EEGLs and SPEGLs for short-term emergency exposures and CEGLs for 90-day continuous exposures to substances. (COT earlier had recommended EEGLs and CEGLs for scores of chemicals in letter reports.)

The Committee's recommendations have been used by the Army, the Navy, and the Air Force as working standards in the absence of standards from the Occupational Safety and Health Administration (OSHA).

Submarine Habitability

From its beginning, a special focus of COT's work for the Navy has been to recommend concentrations of atmospheric contaminants that would be acceptable for a crew working in the closed environment of conventional and nuclear submarines for up to 90 days. Chemicals of interest to the Navy included not only the usual fuels and solvents (e.g., the Freons® used to clean electric generators) but also pesticides, photographic developing chemicals, cigarette smoke, and even the fumes and combustion products of sound- and vibration-damping tiles used in submarines.

In 1969, COT's various recommendations were consolidated in a letter report on the acceptable concentrations of 14 air contaminants, and for several years thereafter, the Committee issued reports on the concentrations of these contaminants actually found in submarines. In 1985, COT established the Subcommittee on Submarine Air Quality with three panels: 1) Panel on EEGLs to develop emergency and continuous exposure guidance levels (EEGLs and CEGLs) for potential contaminants in submarines; 2) Panel on Monitoring to review the analytical techniques used in monitoring submarine contaminants; and 3) Panel on Hyperbarics and Mixtures to study the possible health effects in divers from breathing compressed submarine air. In 1988, the three panels joined in the publication of *Submarine Air Quality: Monitoring the Air in Submarines and Health Effects in Divers of Breathing Submarine Air Under Hyperbaric Conditions*. A copy of *Submarine Air Quality* report has been placed on board every U.S. submarine.

The Panel on EEGLs recommended exposure guidelines for six substances of interest to the Navy: ammonia, hydrogen chloride, lithium bromide, toluene, trichloroethylene, and lithium chromate. The Panel on Monitoring found that cigarette smoke accounted for much of the particulate matter, carbon monoxide, and hydrocarbons in the submarine atmosphere, and it recommended that cigarette smoking in submarines be eliminated. The Panel on Monitoring further recommended that the Navy develop more sensitive and reliable monitoring equipment, as well as better equipment and procedures for dealing with emergencies such as fires. The Panel on Hyperbarics and Mixtures recommended additional research in several areas, including the formation of toxic products during compression and the effects of hyperbaric conditions on the toxicity of contaminants. *Submarine Air Quality* report also recommended that the Navy develop nontoxic paints for use on submarines and that it consider eliminating deep-fat fryers, another source of atmospheric contaminants.

Dioxins

At the request of the General Services Administration (GSA) and NASA, COT investigated the possible risks from chemicals that are released by fires involving polychlorinated biphenyls (PCBs), which are commonly used in electric transformers. The most persistent pyrolysis products are dioxins (polychlorinated dibenzo-*p*-dioxins [PCDDs]); the most toxic and most widely studied form is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD). After a 1979 fire in a NASA office building, GSA and NASA asked COT for a review of dioxin contamination of the building and advice on appropriate remedial action.

The COT Subcommittee on Dioxins reviewed laboratory and epidemiologic data on several major PCDD isomers and related compounds, including their chemistry, toxic mechanisms, and health effects on animals and humans. It also contrasted four risk assessments that had been conducted to establish re-entry standards for office buildings after transformer fires that cause PCDD contamination. The subcommittee recommended adopting the exposure guidelines first developed by the New York State Department of Health, i.e., concentrations of 10 picograms per cubic meter in the air and 25 nanograms per square meter on surfaces, thereby giving GSA and NASA a basis for cleanup action to protect the health of workers. The 1988 report, *Acceptable Levels of Dioxin Contamination in an Office Building Following a Transformer Fire*, also provides agencies and organizations other than the immediate sponsors with guidelines for similar cleanups.

Chromium in Face Masks

The masks used by the Army to detoxify inhaled gases use canisters that contain activated charcoal impregnated with hexavalent chromium, a carcinogen. In 1987, after a congressional inquiry, the Army conducted an internal review of possible health risks associated with using the face masks. It also asked COT to conduct an independent expert review and to recommend further studies or remedial actions for exposed soldiers.

After considering the current information on the toxicologic status of chromium and reviewing the tests conducted by the Army, a COT subcommittee issued the report, *Chromium Contamination in Army Face Masks* (1988). The report concluded that, even under worst-case assumptions, inhalation exposures to insoluble chromium (VI) compounds were well below the current standards or recommendations for the workplace, including those of COT, the National Institute for Occupational Safety and Health, and the DoD. No evidence was found linking exposure to chromium, in any form, with thyroid cancer (the subject of the congressional inquiry). The Committee concluded that no special medical follow-up of military personnel was needed.

Precursors of Munition Chemicals

The Committee on Toxicology has addressed problems of industrial health hazards. In 1987, the Army asked COT to review the literature that had been used as the basis for proposed workplace exposure standards for four precursors of munition chemicals, i.e., methylphosphonic dichloride (DC), methylphosphonic difluoride (DF), pinacolyl alcohol (PA), and O-ethyl-O-(2-diisopropyl-aminoethyl)-methylphosphonite (QL). The precursors were to be produced and packed under Army contract at civilian-operated facilities, and the Office of the Surgeon General of the Army was responsible for protecting workers who were manufacturing or otherwise handling these compounds. Neither OSHA nor ACGIH had developed permissible exposure limits (PELs) or TLVs for these compounds.

The Committee's review uncovered serious gaps in the toxicologic data on the compounds and on several highly toxic by-products. The Committee recommended a number of additional studies to be conducted to provide greater confidence in recommending PELs for these chemicals:

- Developmental, reproductive, and immunotoxicity studies on DC and PA.
- Pharmacokinetic studies on DC.
- Subchronic and cumulative toxicity studies on DF and PA.
- Chronic toxicity studies, including carcinogenicity, on DC, DF, and PA.
- Delayed neurotoxicity studies on QL.

The Committee also recommended specific monitoring and work practices for the chemicals, including measurement; medical surveillance of workers; provision of protective equipment; and the development of procedures for emergency first aid, rescue, spills, and waste disposal.

Insect Repellents

Throughout history, armies have always lost fewer soldiers to combat than to diseases, many of them transmitted by insects. The standard insect repellent used by the U.S. armed forces, *N,N*-diethyl-*m*-toluamide (DEET), developed more than 30 years ago, has never been fully satisfactory. In 1986, the Army asked COT to review its attempts to develop a replacement. The COT report, *Toxicity of Candidate Arthropod Repellents*, has had effects well beyond meeting the needs of its immediate sponsor.

The Army had asked COT to concentrate on a one-step, topical hazard evaluation. The comments and recommendations of COT's Subcommittee on Arthropod Repellents included this step and then were extended to the entire toxicity-testing program. The subcommittee concluded that the overall program was unnecessarily limited and suggested that it be modified in several ways:

- Develop nonhuman models to predict repellent efficacy and toxicity, thus avoiding the need to expose humans to unknown chemicals until toxicity testing in animals is completed.
- Avoid excessive and premature animal testing, especially eye-irritation testing.
- Use *in vitro* test methods for phototoxicity to reduce the number of animals needed for screening.
- Add tests for transdermal absorption, percutaneous toxicity, neurotoxicity, and teratologic effects.
- Reconsider previously rejected materials in light of the less-restrictive approaches.
- Obtain candidate repellents from a wider range of sources, including pharmaceutical companies and university researchers.
- Conduct basic research on insect biting behavior and on human volatile emanations that act as natural repellents or attractants.
- Adhere to EPA guidelines and practices, where possible, to facilitate commercial development of insect repellents tested by the military.

Sponsoring Agencies

In its early days, COT studies and reports were confined to the needs of its original sponsors, the armed services and the Atomic Energy Commission. Most of the reports were issued to the Army, Navy, and Air Force, all of which needed information on the health hazards associated with the many substances to which personnel might be exposed, from the exotic (fuels and explosives) to the mundane (sunscreens and insect repellents).

More recently, COT has accepted requests for assistance from other government agencies, provided that the studies were complementary to the interests of the primary sponsors and could be fit *into* the work schedule. The reports for nonmilitary sponsors address many of the same concerns (and chemicals) as those produced for Department of Defense sponsors, i.e., from varnishes to lubricants and from fungicides to Mace.

Principles of Chemical Risk Assessment

Principles of Risk Assessment: Overview of the Risk Assessment Process

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There are three different approaches to chemical risk assessment which will be considered in this paper. The U.S. Environmental Protection Agency (EPA) Cancer Risk Assessment includes some of the approaches used by the International Agency for Research on Cancer (IARC). The Agency for Toxic Substances and Disease Registry (ATSDR) effort is an evaluated database approach similar to that used in the National Institute for Occupational Safety and Health (NIOSH) Criteria Documents and in the documentations prepared by the Occupational Safety and Health Administration (OSHA) for the Permissible Exposure Limits (PELs) and those of the American Conference of Governmental Industrial Hygienists (ACGIH) for the Threshold Limit Values (TLVs). A third approach is used by the Committee on Toxicology.

Introduction

Although risk assessment, as it is known today, is less than 20 years old, it is derived from that part of toxicology called hazard evaluation which is almost as old as toxicology itself. There are differences, however, between what was done in hazard evaluation and what is done today in risk assessment.

Traditionally, hazard evaluation has been a judgmental decision based on information concerning the agent, the subject, and the exposure. The first step in hazard evaluation is to characterize the toxicity of the agent; this is accomplished by identifying all of the potential adverse effects that can result from either acute or chronic exposure to the agent and by establishing the dose–response relationship for each of these adverse effects. The next step is to determine whether the tox database obtained with the test species is appropriate for the subject or target species and for the actual exposure conditions.

In those cases where the tox data are relevant and where there is a threshold or no-effect level for the specific adverse effect of interest, then the tolerance can be established by simply dividing the No-Observed-Effect Level (NOEL) by an appropriate safety factor. The goal in this approach is to predict a "safe" dose for the target species and, except for those adverse effects for which thresholds cannot be clearly demonstrated, this continues to be the most practical and widely used approach for protecting the health of the public, workers, and military personnel against the adverse effects of exposure to chemicals.

During the early 1970s, there was growing concern about cancer and mutagenesis. Coupled with the creation of the EPA and the growing ability of chemists to detect vanishingly small amounts of environmental contaminants, this concern led to demands for a new approach to risk assessment. Along with many other groups, the National Academy of Sciences/National Research Council (NAS/NRC) was involved in this effort and subsequently issued two reports that had a major impact in this area. One of these was the 1977 report of the Safe Drinking Water Committee, which was sponsored by the EPA, and the other was the 1983 report on Risk Assessment in the Federal Government, which was sponsored by the Food and Drug Administration (FDA). In the second chapter of the first Drinking Water Report, a subcommittee presented an analysis of risk assessment which was "state of the art" at that time. They defined the following four general principles for risk assessment:

1. Effects in animals when properly qualified are applicable to humans.
2. Methods do not exist to establish thresholds for some long-term effects.
3. Use of the maximum tolerated dose (MTD) is a necessary and valid approach to detect carcinogens.
4. Materials should be assessed in terms of their risk rather than as "safe."

These principles plus the recommendations in the report concerning high- to low-dose extrapolation provided the scientific basis for this new approach to risk assessment and set the stage for the second report, which focused on policy and procedures for managing the process of Risk Assessment in the Federal Government. This second report clearly divided risk management from risk assessment and then subdivided risk assessment into four steps: hazard identification, dose–response assessment, exposure assessment, and risk characterization. The latest topic to be added to this classification is risk communication which has also been addressed by a NAS/NRC committee, a Council on Environmental Quality report, and numerous other workshop and

conference reports.

The evolution of risk assessment methodology will undoubtedly continue. At this point in time, there are four areas that should be carefully examined and evaluated.

1. The two approaches to risk assessment — the threshold approach and the extrapolation approach — should be considered to be complementary rather than competing methodologies. The existence or lack of a threshold should determine which approach to use in risk assessment.
2. To improve the threshold approach to risk assessment, safety factors should be used that include appropriate adjustments for differences in kinetics and sensitivity between the test and target species. The concept of a "safe" dose should be replaced with an indication of actual risk.
3. To improve the nonthreshold approach to risk assessment, best estimates rather than upper-bound limits of risk should be provided, and the worst-case assumptions currently used in this approach should be replaced with actual data derived from the target species. The use of kinetic data in this approach is a good first step; however, we must also ensure that the model is capable of dealing appropriately with the relevance of the animal data to the target species and that it addresses such issues as the lack of a dose–response, species differences in susceptibility, and the like.
4. One of the major problems, if not the major problem, with the current state of risk assessment is lack of credibility. Since we often consider some of our predictions to be better than others, we need to develop a good system for communicating this information to the public in a logical and understandable fashion. We need to be able to explain why we are more concerned about Agent A than Agent B even though they have identical Q^* values or GRAS status. We need to convince the public and our peers that it is not the chemical but the dose that determines the risk. It would also help if risk assessors would focus on areas of consenus rather than on confrontation, since the public is confused and justifiably angered when they are sent mixed signals. A good place to start would be to compare the toxicological and epidemiological predictions because these are the two disciplines that contribute most directly to assessing risk from chemical exposure. In those situations where toxicology and epidemiology are giving us different answers, we need to determine why the answers are different and, if possible, to reconcile the difference. In order to accomplish this, we will need to identify and defend all of the assumptions and uncertainties that we have used; we will also need to provide adequate documentation so that the next investigator can replicate the process. If we can do this in a way that is readily understood by the public, we will help them decide whether the risk assessment is a "whitewash" or a "witch hunt."

In conclusion, there is a quote by Albert Einstein that sums it up well. "The right to search for truth implies a duty: One must not conceal any part of what one recognizes to be true."

Issues/State-of-the-Art Methodology for the National Research Council's Committee on Risk Assessment Methods

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The following is the abstract of the presentation by Mr. Goldstein. His paper is not available for publication at this time.

The National Academy of Sciences/National Research Council, through its Board on Environmental Studies and Toxicology in the Commission on Life Sciences, has appointed the Committee on Risk Assessment Methods (CRAM). The Committee was established in response to requests from several U.S. government agencies, including the Environmental Protection Agency, the National Institute for Occupational Safety and Health, the Food and Drug Administration, the National Institute of Environmental Health Sciences, and the Agency for Toxic Substances and Disease Registry. CRAM is also supported in part by the American Industrial Hygiene Association and the American Petroleum Institute.

The 17-member committee has expertise in toxicology, epidemiology, occupational health and medicine, risk assessment, statistics, mathematical modeling, genetics, pathology, biochemistry, and pharmacology. The charge to the committee is to assess the scientific basis, inference assumptions, regulatory uses, and research needs in risk assessment. CRAM will gather information and investigate issues largely through a series of narrowly focused, intensive workshops. CRAM has already organized workshops on Maximum Tolerated Dose, Physiologically-based Pharmacokinetic Modeling, and Two-Stage Carcinogenesis Models. Additional workshops on Use of Epidemiological Information in Risk Assessment and Use of Exposure Information in Risk Assessment are planned in the near future.

CRAM will not only focus on cancer risk assessment but will also address the issue of risk assessments for other end points, such as reproductive and developmental toxicity, neurotoxicity, immunotoxicity, etc. The project which began in 1990 will take three years to complete. Separate reports in a series dealing with each issue will be published. These reports will provide guidance to regulatory decision-makers and risk assessment scientists for developing and employing models for risk assessment.

Principles of Chemical Risk Assessment: The ATSDR Perspective

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Hazardous wastes released into the general environment are of concern to the public and to public health authorities. In response to this concern, the Comprehensive Environmental Response, Compensation, and Liability Act, as amended (commonly called Superfund), was enacted in 1980 to provide a framework for environmental, public health, and legal actions concerning uncontrolled releases of hazardous substances. The Agency for Toxic Substances and Disease Registry (ATSDR) was created by Superfund to address the public health issues of hazardous wastes in the community environment.

Two key Agency programs, Public Health Assessments and Toxicological Profiles, are designed to assess the risk to human health of exposures to hazardous substances that migrate from waste sites or through emergency releases (e.g., chemical spills). The Agency's public health assessment is a structured process that permits ATSDR to identify which waste sites or other point sources require traditional public health actions (e.g., human exposure studies, health studies, registries, health surveillance, health advisories). The ATSDR qualitative public health assessment complements the U.S. Environmental Protection Agency's quantitative risk assessment. For Superfund purposes, both assessments are site-specific. ATSDR's toxicological profiles are prepared for priority hazardous substances found most frequently at Superfund sites. Each profile presents the current toxicologic and human health effects information about the substance being profiled. Each profile also contains Minimal Risk Levels (MRLs), a type of risk assessment value. This paper covers ATSDR's experience in conducting public health assessments and developing MRLs, and it relates this experience to recommendations on how to improve chemical risk assessments.

Introduction

Chemical risk assessments are the source of great activity in government and private sector organizations. Risk assessments on individual chemicals and broad environmental problems have become a staple in regulatory agencies, at both the federal and state levels. Some nonregulatory agencies also conduct risk assessments. The risk assessment approaches and experiences of a nonregulatory, federal, public health agency are the subject of this paper.

The Agency for Toxic Substances and Disease Registry (ATSDR) is one of the eight agencies that constitute the U.S. Public Health Service. Congress created ATSDR in 1980 as part of the Comprehensive Environmental Response, Compensation, and Liability Act (known as Superfund). The Agency was mandated by Superfund to work with the U.S. Environmental Protection Agency (EPA), the states, and the private sector to elucidate the public health consequences of hazardous waste, principally the releases from waste sites covered under Superfund.[1]

What and how we experience things molds our thinking on what represents reality. ATSDR's reality is to work in an emotionally charged area of public health. We often experience high emotions in communities around hazardous waste sites, including some near federal facilities. Our Agency participates in many meetings with community groups who are suspicious of government agencies and generally unimpressed with numbers from numerical risk assessments.

Because of this experience with the public, ATSDR's reality regarding risk assessment can best be described as a somewhat "schizophrenic" existence. We recognize the importance to regulatory agencies of a systematic assessment of risk, and because resources are limited but problems are not, we acknowledge the importance of having a tool that can be used to compare risks. However, we are concerned that the current approach to quantitative risk assessment has not performed very well in many instances — hence our schizophrenia.

This paper outlines the Agency's approach to hazard evaluation of waste sites, proceeding from the complex problem of assessing public hazards posed by individual waste sites to the situation of risk assessment for a single toxicant. ATSDR's public health assessment will be described first.

Public Health Assessments

To set the stage for defining a public health assessment, consider the American public's concern in 1980 that toxic waste in the environment was compromising human health. Moreover, opinion polls in 1991 indicate that this concern continues at the same high level. The public remains fearful

of the health consequences of hazardous waste and toxic substances. Many communities would like — indeed would insist on — a full-scale epidemiologic study of their health. To put this in perspective, EPA now lists 33,000 uncontrolled toxic waste sites in the United States.[2] Using their Hazard Ranking System, EPA ranks each site in terms of its environmental contamination and its ecologic and health significance. The result is called the National Priorities List (NPL) of hazardous waste sites. This list is important because placement on it brings monies from the Superfund trust fund to remediate the site.

The message is that there are very large numbers of uncontrolled — and also controlled — waste sites and facilities in the U.S. that can potentially compromise public health. Given the widespread angst about such sites, a belief is built into the public's mind that EVERY site should be the subject of an intensive, in-depth, health investigation. If the list of most important hazardous waste sites were to number only 2000 and if a community epidemiologic study would cost $2 million or more in today's market, then the cost for such an epidemiological undertaking would be $4 billion. Cost, as well as scientific considerations, lead one to conclude that long-term health studies cannot be conducted at every waste site.

How then does a government public health agency decide which sites (and here we must think in terms of communities of young, elderly, healthy, ill, wealthy, poor, educated, and illiterate human beings) really do require some kind of health action in response to confirmed environmental contamination? ATSDR's instrument for triage in this difficult situation is the public health assessment, or more simply, health assessment.

Definition

ATSDR's public health assessment is "the *evaluation of data and information* [emphasis added] on the release of hazardous substances into the environment in order to assess any current or future impact on public health, develop health advisories or other recommendations, and identify studies or actions needed to evaluate and *mitigate or prevent human health effects* [emphasis added]."[3] In the context of an ATSDR public health assessment, "evaluation of data and information" means employing professional judgments, according to specified guidelines, to characterize the nature and extent of the hazard to human health presented by releases from individual hazardous waste sites. As a federal health agency, we believe that consequential health decisions ought to be predicated on a foundation that permits, indeed encourages, the exercise of professional judgment. The second point of emphasis pertains to the prevention of adverse human health effects. ATSDR uses the public health assessment to identify conditions of exposure to hazardous substances that, when reduced in severity, will prevent morbidity or mortality.

Public Health Assessment Compared with Risk Assessment

ATSDR is often asked how its public health assessment of a waste site differs from an EPA risk assessment for the same site. The implication sometimes is that the two instruments are duplicative and, hence, wasteful. In fact, these two kinds of assessments are complementary, as will be described later; each serves a useful purpose to the agency that utilizes it. But as a hypothetical argument, assume that the risk assessment and the public health assessment are, in fact, fully duplicative. Would the duplication be a waste of resources? To answer this question, consider what happens when a family member is diagnosed as having a fatal disease, resulting in a recommendation for radical clinical intervention. Many people in such situations seek a second medical opinion, sometimes more, because the implications to personal health of being wrong are sometimes too important to rest in the hands of a single medical specialist.

Are hazardous waste sites also worthy of "second opinions"? Given that the average cost of remediating a nonfederal waste site is a multimillion dollar effort, and knowing that public health questions are a serious concern to affected communities, a plausible case can be made for the importance of two opinions, independently derived.

Aside from the foregoing hypothetical argument, an ATSDR public health assessment has several significant distinctions from an EPA risk assessment of the same waste site. These differences are rooted in the respective agencies' needs, policies, and statutory responsibilities. The principal differences are shown in Table I. Both kinds of assessments serve practical purposes and are generally complementary.

Conduct of Public Health Assessments

How do ATSDR and the state health departments conduct public health assessments?[3] The public health assessment is conducted by a multidisciplinary staff using three key databases:

- Environmental contamination data (normally obtained from EPA, sometimes supplemented by data from state agencies, characterize levels of contaminants in environmental media related to the site).
- Health outcome data (normally obtained, when available, from state and local health agencies, e.g., community-specific cancer rates or adverse reproductive outcomes).
- Community health concerns (expressions from the community around the site about their health concerns).

The ATSDR health assessors conduct site visits to obtain a significant amount of these three types of data. Using a weight-of-evidence approach, the health assessors factor the following considerations into their overall assessment of the

TABLE I. Characteristics of ATSDR Health Assessments and EPA Risk Assessments

ATSDR Public Health Assessment	EPA Risk Assessment
• Qualitative, site-specific; uses environmental contamination, health outcomes, and community health concerns data.	• Quantitative, compound-oriented, site-specific; uses environmental contamination data.
• Medical and public health perspectives are weighted to assess health hazards.	• Statistical and/or biologic models are used to calculate numerical estimates of health risks.
• Used to evaluate human health impacts and to identify public health interventions.	• Used to facilitate remediations or other risk management actions.
• May lead to pilot health effects studies, surveillance, epidemiologic studies, or exposure registry.	• May lead to selection of particular remediation measures at a site.
• Is advisory.	• Bears regulatory weight of authority.

public health significance of the site:

- Environmental contamination data are evaluated as follows:
  1. Using existing toxicological information bases, the principal contaminants are identified. Contaminant levels are compared with published environmental media guides derived by ATSDR or with EPA regulatory standards to assess if human exposure to these levels may constitute a public health hazard.
  2. Current and possible future exposure pathways of public health concern are identified. For some sites, models that predict migration of contaminant plumes are used to identify communities at risk of exposure and, on occasion, to attempt to reconstruct the extent of historical exposures.
  3. Special populations at risk of exposure, e.g., children, are identified and, where possible, the extent of their exposure to contaminants of concern is assessed.
- Health outcome data are obtained when they are available and can be focused on a county, community, census tract, or defined area around the site. This approach produces a broad picture of the health status of a community that may have experienced toxic releases. The data *do not* represent an epidemiologic evaluation of the community at risk. That type of refinement occurs through follow-up studies whenever the public health assessment identifies the need. In addition, health outcome data are an important tool the Agency uses to address concerns about excess disease occurrence in communities living near a waste site.
- Community health concerns are obtained by establishing contact with citizens' groups, local healthcare providers, and community leaders. These types of data serve two purposes. First, by reaching out to the community, a contact is made that begins a health communication and education effort that must attend every public health assessment. Second, some health data or other pertinent site-specific information may be unrecognized by health authorities, but known to the citizens.

From the public health assessment will come a ranking of the site in terms of its overall significance to public health. ATSDR currently uses five categories of importance (with Agency Actions for each category): A: Urgent Public Health Hazard (health advisory); B: Public Health Hazard (health follow-up); C: Indeterminate Public Health Hazard (possible health follow-up, identify gaps); D: No Apparent Public Health Hazard (environmental health education, monitoring and revisit); and E: No Public Health Hazard (no actions by ATSDR).[3] The specific actions for each site are determined by an intra-agency panel, implemented by designated divisions, and monitored by the intra-agency panel. Besides guiding ATSDR as to which sites require follow-up health actions, the site classifications are one factor considered by EPA to set priorities of sites for remediation.

Based on the site-specific recommendations made, each health assessment identifies what health actions are to be undertaken. The actions range from health studies carried out by ATSDR, often in cooperation with state health departments, to actions related to preventing exposure by EPA's restricting access to contaminated areas, if access had not already been restricted.

Legal Requirements

Superfund directs ATSDR to conduct a public health assessment of every site that is proposed for, or placed on, EPA's NPL within 1 year of its proposal or placement. Of the 1292 sites currently on the NPL, about 10% are federal sites or facilities. More specifically, 97 sites on the current NPL are Department of Defense (DoD) sites; another 17 are Department of Energy (DoE) facilities; and 1 site is currently split between DoD and DoE. There are five other NPL sites under federal responsibility (the Department of Transportation and the Department of Interior, two each; and the Small

Business Administration, one). Through interagency agreements, ATSDR has begun receiving the financial resources necessary to undertake Public Health Assessments of DoD and DoE sites and facilities. Because considerable environmental contamination may have occurred around some federal sites, the public health assessments will be difficult and their conduct protracted.

In addition to mandating public health assessments of NPL sites, Superfund permits individuals to petition ATSDR to conduct these assessments for sites of concern to them. This brings government resources to address the concerns of individual citizens. ATSDR has received approximately 150 petitions since 1987 and has accepted about 70% for the conduct of public health assessments. (Petitions are rejected when evidence is lacking of any actual or potential releases of hazardous substances.) Approximately 55% of petitions have come from individual citizens; the remainder have been submitted from members of Congress, attorneys, local elected officials, and state/local health departments. ATSDR anticipates the number of petitions will increase as awareness of the petitioning mechanism grows.

Also, under Section 3019 of the Resource Conservation and Recovery Act (RCRA) amendments of 1984, ATSDR can conduct a public health assessment of a RCRA facility if requested by EPA, a state, or an individual. However, statutory language requires that the request for a public health assessment be accompanied by funds. ATSDR has conducted very few public health assessments of RCRA facilities, approximately one dozen to date. This number is too low to permit any generalizations.

Findings from Public Health Assessments

The ATSDR public health assessment database contains information that is useful in assessing the overall extent of adverse health effects associated with releases of hazardous substances. The database contains information about substances released from individual sites and facilities, citizens' health concerns, and some health data from state and local health departments. ATSDR is currently consolidating its databases into a single, comprehensive database called HAZDAT to probe associations between releases of hazardous substances and health outcomes. The Agency anticipates that HAZDAT will be available to the public in 1992.

Drawing on various Agency reports and documents, it is possible to summarize some of the principal findings to date from the large number of public health assessments conducted.[4,5] More detailed analyses will be available when the HAZDAT information base is fully operational.

Public Health Assessments and Consultations

- The majority of NPL sites on the list through 1988 are either industrial sites (31%) or landfills (30%).
- Several volatile organic chemicals (e.g., trichloroethylene, benzene, tetrachloroethylene) and metals (e.g., lead, chromium, arsenic) are the substances most often identified at the sites as potential contaminants of concern to health.
- Overall, ATSDR estimates that 4.1 million people live within 1-mile radii of the 725 sites for which population data were available, resulting in an average of about 5700 persons within 1 mile of each site. (This figure should be understood in terms of its limitations. For some sites, not all persons within a 1-mile radius are at risk of exposure, depending on migration patterns of substances released. In addition, for some sites, the population at risk of exposure extends beyond a 1-mile radius where there is documented groundwater contamination.) EPA estimates that approximately 41 million people live within 4 miles of a Superfund site.[6]
- Using data available in 1988, ATSDR reported that conditions and exposure potentials at 109 of the 951 sites then on the NPL were considered to constitute ongoing or probable public health concerns, a health follow-up rate of about 11.5%.[4] During 1990, ATSDR implemented a more intensive health action analysis. Of the 261 sites reviewed in fiscal year 1991, 38% were identified as requiring some kind of health action.
- Because of their recreational activities and their propensity for hand-to-mouth activities, children less than 6 years of age are at increased risk of exposure to contaminants in dirt and dusts, compared with older children and adults. Boys are more likely than girls to come into contact with soil-laden contamination.
- Where off-site migration of hazardous substances occurred, groundwater was often contaminated. For example, using data available to ATSDR in 1988, groundwater was contaminated at 71% of sites with documented evidence of migration of metals and at 88% of sites with such evidence for volatile organic chemicals. Evidence of lead migration into groundwater was detected at about 17% of all NPL sites, based on health assessment data from 951 NPL sites.
- Working with state agencies, ATSDR has found that the overall assessment of potential health consequences from historical exposures to hazardous substances is a matter of considerable public health importance. For example, the Agency is working with one state health department to advise young women whose prior exposure to lead could result in endogenous releases of lead during pregnancy.
- ATSDR's health consultations confirm that acute, adverse health effects are commonly reported fol-

lowing emergency releases of hazardous substances. Eye irritation, dermatologic effects, respiratory problems, and a variety of neurologic complaints constitute the bulk of these acute health problems.

- Preliminary findings from a surveillance system of emergency events indicate that two-thirds of hazardous substance releases occur from stationary facilities; one-third occur from moving equipment.
- ATSDR's public health assessment experience indicates that large numbers of minorities live near hazardous waste sites. A report from a public interest group suggests that minorities are more than three times as likely as white Americans to live near hazardous waste sites.[7] The Agency is currently developing demographic data about who lives around Superfund sites.

Health Investigations and Registries

ATSDR's public health assessments are linked to investigations of the effects of hazardous substances on the etiology of chronic disease and acute, adverse health effects. ATSDR has identified seven Superfund Priority Health Conditions that will be the focus of health investigations by the Agency, university researchers, and state health investigators. The seven conditions were identified through a comprehensive analysis of the literature on toxicologic and human health effects associated with known Superfund hazardous substances (Table II).

In 1987, in cooperation with state agencies, ATSDR undertook a series of human exposure assessments, surveillance projects, and epidemiologic health investigations of persons who may be at increased risk of exposure to hazardous substances released from waste sites. To date, the Agency has conducted 37 pilot health studies (principally exposure assessments), 18 epidemiology investigations, and 20 surveillance projects. The aggregate findings from this work are currently being evaluated.

In general, average biological exposure levels have been low compared with occupational exposures to the same substances. However, the Agency has found that each exposure assessment must consider the distribution of all exposures within the community investigated, not relying simply on the mean or median value.[8] Where individuals exceed health-based exposure standards or guidelines, ATSDR works with state and local authorities to reduce the exposure for those individuals.

TABLE II. ATSDR's Superfund Priority Health Conditions in Alphabetical Order

Birth defects and reproductive disorders
Cancers (select)
Immune function disorders
Kidney dysfunction
Liver dysfunction
Lung and respiratory diseases
Neurotoxic disorders

TABLE III. Top-Ten Superfund Hazardous Substances*

1. Lead	6. Cadmium
2. Arsenic	7. Polychlorinated biphenyls
3. Mercury	8. Chloroform
4. Vinyl chloride	9. Benzo(b)fluoranthene
5. Benzene	10. Trichloroethylene

*Note: These are the top 10 substances from the list of 275 prioritized substances.[9]

ATSDR's national exposure registry program promises new, important information on the health effects of long-term exposure to low concentrations of hazardous substances. The exposure registry is a listing, along with health status information, of persons who have had exposure to a hazardous substance of primary interest, at exposure levels of concern. Such registries can be evaluated over time to assess health trends. Currently, the Agency has established national subregistries of persons exposed to dioxin (4 NPL sites) and trichloroethylene (13 NPL sites), has initiated a subregistry of persons exposed to benzene, and has plans for a chromium subregistry. The Agency considers the national exposure registry of great importance for determining the health effects of long-term exposure to hazardous substances.

Risk Assessments of Individual Chemicals

ATSDR public health assessments for individual hazardous waste sites usually involve the presence of mixtures of hazardous substances. In addition, ATSDR develops risk assessment estimates for individual chemicals. These risk estimates are for substances prioritized jointly by ATSDR and EPA. Substances are ranked by frequency at NPL sites, inherent toxicity, and likelihood for human exposure. Currently, 275 substances have been ranked.[9] (The top ten substances are listed in Table III.)

For each substance, Superfund requires that ATSDR develop a toxicological profile and make it available to the public. Each profile must describe what is known about a substance's toxicity and human health effects. In addition, determinations as to the levels of exposure that present a significant risk to human health, e.g., Significant Human Exposure Levels (SHELs), must be provided in each profile. ATSDR is currently addressing the development and dissemination of SHELs by determining Minimal Risk Levels.

Minimal Risk Levels

The ATSDR Minimal Risk Level (MRL) is defined as "an estimate of the daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse, noncancerous effects over a specified duration of exposure."[10] Inhalation MRLs are exposure concentrations

expressed in parts per million for gases and volatile substances or milligrams per cubic meter for particles. Oral MRLs are expressed as daily human doses of mg/kg/day. ATSDR does not derive MRLs for dermal exposure, owing to lack of methodology to develop them. The purpose of these estimates is to provide health professionals with a concept of levels at which adverse health effects are not expected to occur in humans. They are not meant to support regulatory action, but the MRL should serve as an advisory that physicians and public health officials can consider when making recommendations to protect populations living in the vicinity of hazardous waste sites or chemical emissions. ATSDR considers such values as an adjunct to the overall context in which decisions regarding health issues are made, rather than a "pivot point" for such decisions.

Because chemicals may elicit more than one toxic effect, ATSDR attempts to determine the critical effect in the target organ, i.e., the first adverse effect or its known precursor that occurs as the dose increases. The critical effect for a given exposure duration and route is determined only after assessing the scope of the database and the quality of all studies identifying effects by the route of exposure being considered. If the most sensitive target system cannot be identified, the critical effect cannot be determined. It follows that a MRL cannot be derived from this database.

When the critical effect for the route and duration has been identified, MRLs are derived from the no-observed-adverse-effect level (NOAEL). In lieu of a NOAEL, an uncertainty factor (UF) of 10 is employed for use of a lowest-observed-adverse-effect level (LOAEL). Additional UFs of 10 may be employed for animal-to-human and human-to-human extrapolations. MRLs can, therefore, have uncertainty factors ranging from 10 (data derived from humans) to 1000 (derived from animal LOAELs). MRLs are derived using the following formula.

$$\text{MRL} = \frac{\text{NOAEL}}{\text{UF}}$$

The determination of ATSDR's MRLs relies heavily on the same methodology used to derive the EPA Reference Risk Dose (RfD). Moreover, personnel from both agencies serve on work groups that develop each of these numbers.

However, there are some key differences between MRLs and RfDs. ATSDR develops MRLs for acute, intermediate, and chronic exposure durations and for both oral and inhalation routes of exposure. EPA develops its verified RfDs for chronic oral and Reference Concentrations (RfCs) for inhalation exposures. It is current ATSDR policy not to extrapolate data across routes and durations of exposure; rather, pharmacokinetic data are used to bridge these kinds of extrapolations, if such data are available.

MRLs are not applicable to nonthreshold effects such as genotoxicity and cancer. The Agency accepts the categories of carcinogens as published by the Department of Health and Human Services, the International Agency for Research on Cancer, and the EPA. It is Agency policy to prevent or mitigate any human exposure to an identified carcinogen.

The Agency has prepared *Toxicological Profiles* for 130 substances. A potential exists for the derivation of 780 MRLs for the three duration and two exposure categories. To date, 187 MRLs have been developed and are found in individual Agency toxicological profiles. As can be inferred, the Agency's scientists found database inadequacies that prohibited the development of many MRLs. These inadequacies circumscribe the health assessor's opportunity to fully evaluate the potential health effects posed by hazardous substances at a site or release.

Superfund directs ATSDR to initiate a program of research to fill data needs for priority hazardous substances. ATSDR initiated the program in 1991 through an announcement of the data needs for 38 priority substances.[11] As an example, ATSDR identified key data needs for arsenic to be 1) comparative toxicokinetics, 2) determination of half-lives in surface water and groundwater, and 3) bioavailability from soil. The findings from this program of research should be quite useful in improving the scientific database used in chemical risk assessment.

ATSDR's experience in developing MRLs has led to some observations about the process. One key observation is the problem of data quality. What constitutes acceptable data? How does a governmental agency assess the adequacy of experimental investigations, assurance of data quality, and confidence in interpretation of findings by investigators whose work may be crucial for determining an MRL? Any risk assessor faces this question in a variety of ways. Currently, no agreed-upon standards are available, and the subject of data quality is currently being discussed by the World Health Organization's International Program on Chemical Safety and various national agencies.

Recommendations for Improving Chemical Risk Assessments

Based on its experiences conducting public health assessments of Superfund sites and deriving MRLs for substances in its toxicological profiles, together with the involvement of its technical staff in developing risk assessment policies and procedures at federal and state levels, ATSDR recommends the following to improve risk assessments of individual chemicals.

- Risk assessments should state clearly the key assumptions, uncertainties, and limitations inherent in conducting each risk assessment. This information should be routinely provided to the risk manager and to other users of the risk assessment. Consideration might be given to presenting risk as a range rather than as a single point estimate.
- The science undergirding risk assessment must be

improved through a program of directed research. In particular, priority should be given to research on human exposure assessment, pharmacokinetics, extrapolations between species and between routes of exposure, and basic mechanisms of toxicity. It is important that the methods required for utilizations of these kinds of data in the context of risk analysis should be a component of this directed research.

- Weight-of-evidence and weight-of-judgment should be included in conducting risk assessments. Also, consideration should be given to "negative-outcome" studies as well as those with positive outcomes.
- Models that have not been validated with experimental data should be viewed skeptically. This suggests the increased use of biologically based risk assessments.
- Agencies should consider adopting independent, scientific, peer review of risk assessments and providing draft versions to the public for review and reaction. ATSDR practices both of these actions when developing its toxicological profiles and other reports. These actions enhance the scientific quality of risk assessments, in ATSDR's experience.
- In the absence of adequate scientific information, a risk assessment should not be done. All risk assessments acquire a certain degree of permanency, and those that are poorly developed are difficult to retract or revise and lead to diminished credibility of the risk assessor. Rather than developing a risk assessment predicated on an insecure foundation, it is better to identify and conduct the key research needed to perform a specific risk assessment.

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Risk Assessment for Noncarcinogenic Chemical Effects

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The fundamental assumption that thresholds exist for noncarcinogenic toxic effects of chemicals is reviewed; this assumption forms the basis for the no-observed-effect level/safety-factor (NOEL/SF) approach to risk assessment for such effects. The origin and evolution of the NOEL/SF approach are traced, and its limitations are discussed. The recently proposed use of dose–response modeling to estimate a benchmark dose as a replacement for the NOEL is explained. The possibility of expanding dose–response modeling of noncarcinogenic effects to include the estimation of assumed thresholds is discussed. A new method for conversion of quantitative toxic responses to a probability scale for risk assessment via dose–response modeling is outlined.

Introduction

Risk assessment for toxic chemicals that do not induce carcinogenic or mutagenic effects has traditionally been based on the fundamental assumption that there are levels of exposure for such agents below which adverse health effects will not occur, even if exposure is long term (Figure 1). Biological underpinnings for this "threshold" concept include the fact that the toxicity of many chemicals is manifest in exposed subjects only after the depletion of a known physiological reserve and that the biological repair capacity of many organisms can accommodate a certain degree of damage by reversible toxic processes.[1,2] The objective of risk assessment for noncarcinogenic chemical effects has thus been to establish a "threshold dose" below which adverse health effects are not expected to occur.

The NOEL/Safety Factor Approach

The classical approach to risk assessment for noncarcinogenic chemical effects is commonly believed to have originated with the setting of safe levels of food additives. Establishment of the acceptable daily intake (ADI) by the formula

$$ADI = \frac{NOEL}{SF}$$

evolved from the work of Lehman and Fitzhugh,[3] who wrote about "attempts to predict the safety of a proposed food additive to humans in terms of toxicity in animals." Here NOEL stands for no-observed-effect level, a term derived from what Lehman and Fitzhugh called "that dose just short of causing an observable effect," and SF stands for safety factor, a quantity applied in order to allow for uncertainties in extrapolating from animals to humans.

The term NOEL as used today may be defined loosely as the highest experimental dose level (or human exposure level) at which adverse effects are not observed (Figure 2). Generally, individual NOELs are established for individual toxic effects. The original SF proposed by Lehman and Fitzhugh[3] was 100, which represented a factor of 10 to allow for differences in sensitivity to the test agent in humans as compared to experimental animals (interspecies), and a factor of 10 for variation in sensitivity within the human population (intraspecies). The 100-fold safety factor gained acceptance over time.[4,5]

Modifications to the NOEL/SF Approach

In 1977, the National Research Council's Safe Drinking Water Committee[6] recommended several changes in the setting of ADIs. It proposed that the NOEL be expressed on a body weight basis (mg/kg body weight) rather than a dietary

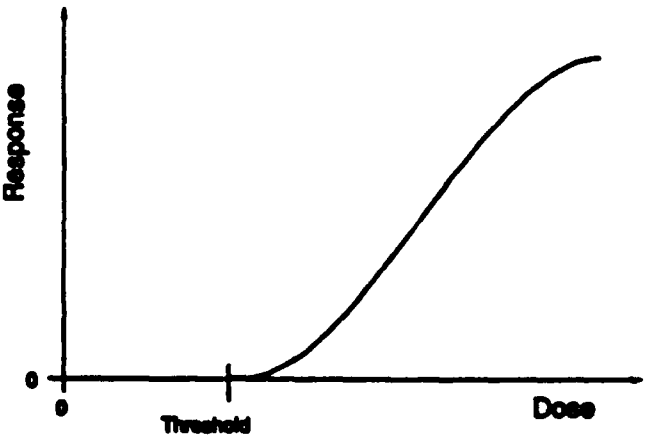

FIGURE 1. Threshold concept.

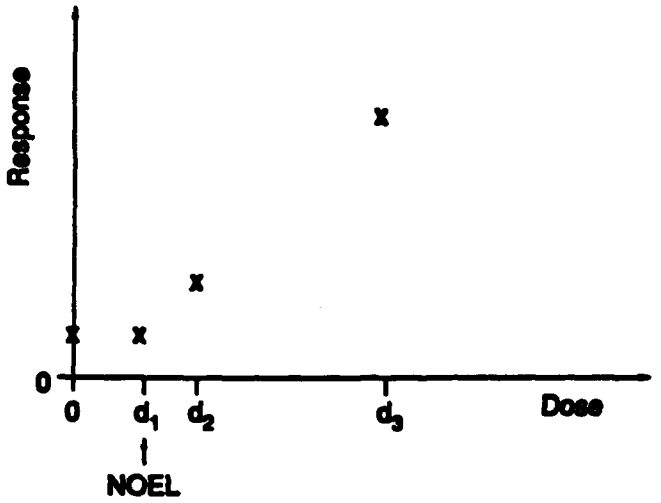

FIGURE 2. No-observed-effect level (NOEL).

percentage basis (mg/kg diet). The Committee also endorsed the reduction of the 100-fold safety factor to only 10-fold if the NOEL was based on human data but recommended that the safety factor be increased to 1000-fold if toxicity data were inadequate to establish a NOEL.

Although the NOEL/SF approach has been and still is popular in regulatory toxicology, it is subject to serious scientific limitations. Smaller, less sensitive experiments tend to yield larger NOELs and, hence, larger ADIs than larger, more sensitive experiments.[7,8] Safety factors of 10-fold for intraspecies and interspecies conversions are somewhat arbitrary and cannot be guaranteed to provide absolute assurance of safety[9] (Figure 2).

In recognition of the above limitations, the U.S. Environmental Protection Agency (EPA) recently recommended several changes in the setting of acceptable levels for toxic effects other than carcinogenicity.[10,11] Instead of calculating an ADI, the EPA[10] recommended that a "reference dose" (RfD) be established according to the expression

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF} \times \text{MF}}$$

where: NOAEL = no-observed-adverse-effect level (meaning failure to achieve statistical significance)

UF = uncertainty factor as opposed to a safety factor

MF = modifying factor to be used in cases of scientific uncertainties about the data

The UF is a composite of 10-fold factors for interspecies and intraspecies uncertainties, uncertainties in extrapolating from subchronic to chronic effects, and uncertainty associated with the use of a LOAEL (lowest-observed-adverse-effect level) in cases when a NOAEL cannot be identified.[11] In addition to these sources of uncertainty, the National Research Council's Committee on Toxicology[12] routinely considers differences in route of exposure in determining the size of appropriate safety factors; the EPA does not.

If the level of a toxic agent to which humans are already exposed or are likely to be exposed is known or can be estimated, and the degree of safety associated with such a level is desired, then the application is simply reversed. In such a case, the potential risk to humans is assessed by calculating a margin of safety (MS) defined by

$$\text{MS} = \frac{\text{NOAEL}}{\text{HEL}}$$

where: HEL = human exposure level

Explicit Risk Estimation

Although the potential for dose–response modeling of both quantal and quantitative noncarcinogenic toxic responses was illustrated by the Safe Drinking Water Committee of the National Research Council,[13] it did not recommend changing from the NOEL/SF approach for the assessment of noncarcinogenic hazards. Recently, however, efforts have been made in the area of statistical modeling of such adverse health effects in order to exploit the shape of the dose–response curve and to account for the precision of estimates of acceptable levels of chemicals.

The concept of a benchmark dose (BD) has been proposed as a replacement for the NOAEL.[8,9] The BD is defined as a statistical lower confidence limit on the dose producing some predetermined, relatively small increase in response rate (risk), such as 0.01 or 0.1 (Figure 3). The BD is promoted as representing a toxicologically relevant quantity because it is defined in the spirit of a LOAEL, although it is not usually an experimental dose level. It makes appropriate use of the sample size, as reflected in the magnitude of the confidence limit. The BD exploits the shape (steepness)

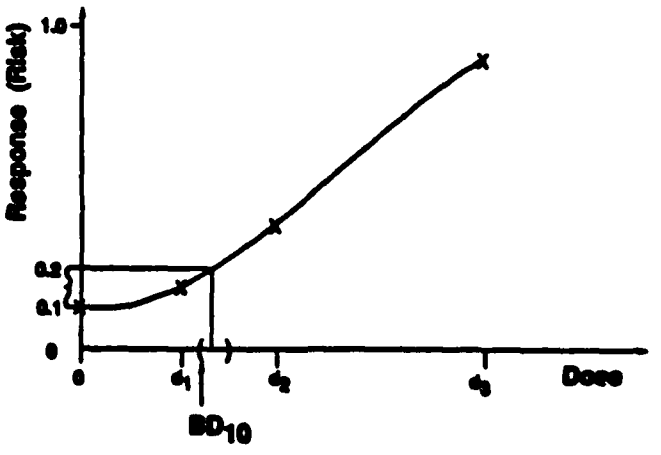

FIGURE 3. Benchmark dose (BD).

of the dose–response curve in the experimental range; however, it does not depend strongly on the particular statistical model used because the model is not followed below the 1% response level.

Crump[9] has recommended redefinition of the ADI according to

$$\text{ADI} = \frac{\text{BD}}{\text{SF}}$$

Gaylor[8] proposed that the BD could be used to determine the size of the SF needed to achieve a desired low level of risk. In this sense, Gaylor argued that setting an acceptable level of a chemical by dividing a BD by a SF was equivalent to linear, low-dose extrapolation. EPA is currently proposing the BD/SF approach for setting levels of reproductive and developmental toxicants.

Modeling Quantal Responses

The primary effort in dose–response modeling of quantal toxic responses has been for reproductive and developmental adverse effects.[14–17] By way of illustration, Chen and Kodell[16] employed a Weibull dose–response model for prediction of toxic effects and a beta-binomial probability distribution to account for intralitter correlation of fetuses. For quantitative risk assessment, they recommended linear extrapolation below the BD-LED01, i.e., the BD that corresponds to 1% excess risk above background risk. Thus, the dose–response model was proposed specifically to improve the estimation of a BD, rather than as a tool for extrapolation far below the data range.

In an effort to translate the threshold concept underlying the NOEL/SF approach to the more quantitative approach offered by statistical modeling, Kodell et al.[18] proposed a threshold model for reproductive and developmental toxicity. If a threshold is assumed to exist, it can be estimated by way of statistical dose–response modeling (Figure 4). However,

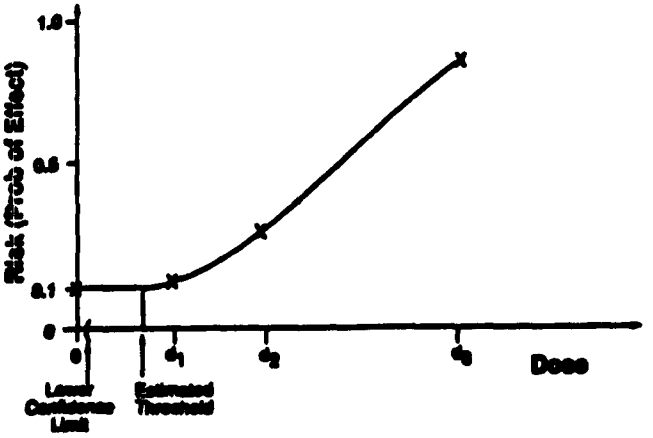

FIGURE 4. Estimation of threshold.

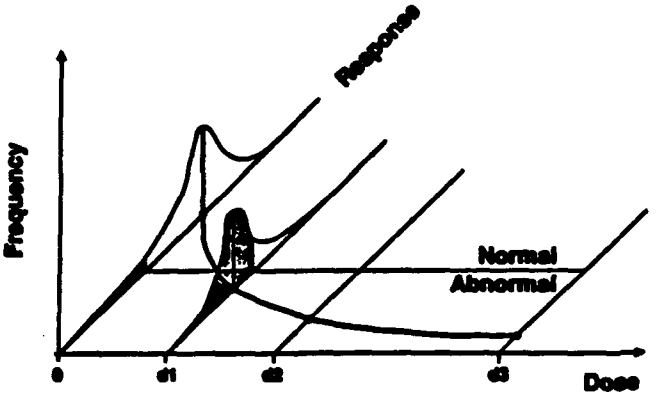

FIGURE 5. Modeling quantitative (continuous) responses.

as pointed out by Kodell et al.,[18] such modeling cannot of itself be used to establish the existence or nonexistence of true thresholds. Whereas, the lower confidence limit on an assumed threshold might often be zero even when a nonzero threshold value is estimated in the best-fitting model, simply including the possibility of a threshold in a dose–response model will tend to give higher BDs than excluding the possibility of a threshold altogether. Even with estimated thresholds, safety factors are necessary to account for uncertainties in interspecies and intraspecies differences.

Modeling Quantitative Responses

Unlike traditional, quantal, teratologic responses, many toxic responses are quantitative in nature. Some examples include organ and body weights, survival time, clinical chemistry and hematology measurements, neurological effects, and behavioral effects. For risk estimation, these response variables must be transformed to a probability scale. Then a BD can be calculated and used for risk assessment.

A fundamental approach to risk assessment for quantitative responses has been proposed by Gaylor and Slikker[19] and further developed by Chen and Gaylor.[20] In short, the process involves four basic steps. First, a dose–response relationship for the expected value of a given quantitative end point must be postulated. Next, a statistical distribution of individual measurements about the dose–response curve (e.g., normal) must be assumed. Third, an abnormal or adverse range of the distribution for the given end point must be defined, e.g., a low percentage point, perhaps 1%, of the distribution in control subjects. Finally, the previous three steps are combined to calculate the probability (risk) of an adverse effect as a function of dose (Figure 5). As with the quantal response models discussed above, the dose–response model for quantitative responses is used to improve the estimation of a BD at the lower extreme of the data range; it is not for extrapolation below that point.

Summary

Classical risk assessment for noncarcinogenic chemical effects has assumed that chemical levels associated with zero risk can be identified, i.e., it has been threshold-based. This is evidenced by the use of NOELs as representing safe levels for particular test species. Sources of uncertainty with respect to characterizing human risk based on animal data have been recognized from the beginning, as indicated by the use of safety factors in converting animal NOELs to acceptable human exposure levels. The passage of time has seen the incorporation of additional sources of uncertainty into safety factors used in the risk assessment process. In addition, a movement has begun toward explicit risk estimation for both quantal and quantitative toxic responses through the use of dose–response modeling. This modeling has had as its purpose the estimation of a BD to replace the NOEL, as opposed to low-dose extrapolation per se. Some models have included the possibility of a threshold, in the spirit of the NOEL approach, in order to exploit underlying biological theory, where justified.

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Issues in the Science and Methodology of Chemical Risk Assessment

Methodologic Issues in Using Epidemiologic Studies for Quantitative Risk Assessment

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Although animal studies have been used most often for quantitative risk assessment, it is generally recognized that well-conducted epidemiologic studies would provide the best basis for estimating human risk. However, there are several features related to the design and analysis of epidemiologic studies that frequently limit their usefulness for quantitating risks. The lack of accurate information on exposure in epidemiologic studies is perhaps the most frequently cited limitation of these studies for risk assessment. However, other features of epidemiologic study design, such as statistical power, length of follow-up, confounding, and effect modification, may also limit the inferences that can be drawn from these studies. Furthermore, even when the aforementioned limitations are overcome, substantial uncertainty exists concerning the choice of an appropriate statistical (or biologic) model for extrapolation beyond the range of exposures observed in a particular study. This paper focuses on presenting a review and discussion of the methodologic issues involved in using epidemiologic studies for risk assessment. This review concentrates on the use of retrospective, cohort, mortality studies of occupational groups for assessing cancer risk because this is the most common application of epidemiologic data for quantitative risk assessment (QRA). Epidemiologic data should not be viewed as a panacea for the problems inherent in using animal bioassay data for QRA. Rather, information that can be derived from epidemiologic and toxicologic studies complement one another, and both data sources need to be used to provide the best characterization of human risk.

Introduction

Risk assessment is an emerging discipline that involves the characterization of risks from human exposures to environmental or occupational hazards. The process has been defined as having the following four steps: 1) identification of hazards, 2) exposure assessment, 3) estimation of dose–response relationships, and 4) the characterization of risk. The numerical quantification of the risk associated with human exposures has been generally referred to as quantitative risk assessment (QRA).[1]

To date, most risk assessments have been based upon analyses of animal bioassay data. Considerable uncertainty generally surrounds risk estimates derived from analyses of animal studies because of the need to extrapolate between species and from the relatively high doses administered to animals to the relatively low levels of human exposures.

These uncertainties have led some authors to question the relevance of data from experiments in which animals are exposed to high doses for predicting human risk[2] and to suggest reliance on epidemiologic data for QRA. Other researchers have demonstrated a reasonably strong correlation between cancer potency estimates derived from assessments based on toxicologic and epidemiologic data[3,4] supporting the validity of using animal bioassay data for predicting human risk.

Despite the uncertainties described above, there will continue to be a need to perform QRAs based on animal bioassay data. The alternative is to wait until greatly improved epidemiologic information is developed, which is socially unacceptable. Furthermore, because of the nonexperimental nature of epidemiologic investigations, data from these studies have their own limitations that may often introduce additional uncertainties into the risk assessment process. The purpose of this paper is to provide a review of the key methodologic issues and attendant uncertainties related to the design and analysis of epidemiologic studies for QRA. This discussion will primarily focus on the use of retrospective, cohort, mortality studies of occupational groups for assessing cancer risk because this is the most common application of epidemiologic data for QRA.

Study Design

In contrast to experimental studies in animals, the observational nature of epidemiologic investigations generally introduces numerous sources of uncertainty into the QRA process. Unlike toxicologists, epidemiologists generally cannot randomly assign exposures to the toxic agent under study, nor can they limit exposures to other potential disease risk factors that may bias and otherwise distort the relationship between exposure and disease. Risk assessors need to be cognizant of the following issues related to the design of epidemiologic studies, which may introduce substantial uncertainties into the QRA process.

Exposure and Dose Estimation

The lack of adequate information on exposure is the most frequently cited reason for rejecting epidemiologic data as the basis for QRA. This is particularly a problem for retrospective, cohort, mortality studies of occupational groups because information on levels of exposure is frequently lacking during the early time periods of these studies. This situation may improve as companies increase their routine collection of data on occupational exposures. Considerable progress has also been made in developing better methods for estimating historical exposures in the workplace.[5]

Even if only crude estimates of exposures are available, epidemiologic data can still be useful for QRA. At the very least, if a range of likely exposures can be estimated for an epidemiologic study, then a range of possible risk estimates can also be derived from the study. This range of risk estimates can then be used to check whether the estimates derived from an animal-based model appear to be reasonable, i.e., are they in the range of the possible epidemiologic estimates.

Ideally, information on doses to the target tissues should be used for performing QRA using epidemiologic and animal bioassay data. If the target tissue dose is a linear function of the external exposure, then use of the external exposure is appropriate for QRA. However, if one needs to extrapolate beyond the range of the epidemiologic data, then use of the external exposure may produce unrealistic estimates of risk if the relationship between external exposure and target tissue dose is nonlinear. Moreover, extrapolations from models based on epidemiologic data may be undermined by physiologic and other differences within the human population unless estimates of dose rather than exposure are used for the assessment. For example, a model based on a study of the effects of respiratory exposures in a working male population could not be validly used for predicting risk to a nonworking female population unless dosimetric adjustments were made for factors such as differences in ventilation rates.

Direct measurements of target tissue doses will rarely (if ever) be available in occupational, cohort, mortality studies. However, physiologically and pharmacologically based models have recently been applied to the estimation of target tissue doses to improve extrapolations from animal studies to predict human risk.[6] These models may also find applications for improving risk estimation based on epidemiologic studies. In addition, biological markers, such as DNA and protein adducts, may also be useful for estimating at the molecular level the dose to target tissues in epidemiologic risk assessments.[7,8]

The potential influence of exposure misclassification on risk estimates derived from epidemiologic studies is an area requiring additional investigation. It is often assumed that nondifferential misclassification of exposure will result in a weakening of the dose–response relationship and, thus, an underestimation of the risk associated with exposures. However, it has been shown that exposure misclassification may result in biased risk estimates in either direction.[9,10]

Confounding

Perhaps the greatest obstacle toward utilizing epidemiologic studies for risk assessment is the potential for confounding by other risk factors. Confounding is the mixing of effects in which the estimate of the effect of exposure is distorted by the effect of an extraneous factor.[11] In occupational, cohort, mortality studies, potential confounding frequently exists due to the presence of multiple exposures found in the workplace or due to differences between the study population and the referent population in terms of personal risk factors (e.g., smoking).

Confounding in experimental (i.e., animal) studies is effectively limited (although not eliminated) by randomization of exposure. In nonexperimental (i.e., epidemiologic) studies in which randomization of exposure is not performed, confounding variables may not be randomly distributed between the exposed and nonexposed groups. Although the influence of measured confounders may be controlled for in the analysis of epidemiologic studies, the possibility of confounding by unmeasured confounders can never be fully eliminated. Greenland[12] has also emphasized that the failure to randomize and the resulting potential for confounding in epidemiologic studies undermines the interpretability of the inferential statistics that are generally used in these studies (i.e., p values and confidence intervals). Thus, the true uncertainty in the results from epidemiologic studies may not be fully estimable because of unrecognized confounding.

Effect Modification

Effect modification (interaction) in epidemiologic studies is also an important consideration for QRA. Effect modification refers to a change in the magnitude of an effect measure (e.g., rate ratio) according to the value of an additional variable.[11] The risks in occupational cohort studies may be modified by related, time-dependent covariates such as age at first exposure, time since first exposure (empirical induction period), or time since last exposure; risks may also be modified by personal habits such as cigarette smoking or by other exposures found in the workplace. When recognized and properly analyzed, effect modification may be viewed as an advantage of epidemiologic data over animal bioassay data for QRA because it provides information on how exposures interact in the real world. However, unrecognized effect modification may introduce additional uncertainties into the extrapolation of the results from an epidemiologic study to other populations in QRA.

Sample Size and Statistical Power

Epidemiologic studies are relatively insensitive for

TABLE I. Sample Size Estimates for Detecting Varying Levels of Excess Lung Cancer Risk in a Hypothetical, Retrospective, Cohort, Mortality Study

Assumed Excess Risk	Relative Risk (SMR)[A]	Expected Deaths[B]	Person Years[C]	Number of Workers[D]
10^{-2}	1.20	170	217,161	4,343
10^{-3}	1.02	15,605	2.0×10^{7}	399×605
10^{-4}	1.002	1.5×10^{8}	2.0×10^{9}	39.6×10^{6}
10^{-5}	1.0002	1.5×10^{9}	2.0×10^{11}	39.6×10^{10}

[A]Relative risks calculated using a background risk (cumulative probability) of 0.06 for developing lung cancer for males over age 15, based upon the proportion of deaths from lung cancer among U.S. males over age 15 in 1982.[13]

[B]Expected number of deaths calculated using formula from Beaumont and Breslow,[14] assuming 80% power $(1-\beta)$, α level of 0.05 (1-tail), and the calculated relative risk.

[C]Person-years calculated by dividing the expected number of deaths by the lung cancer rate (7.8×10^{-4}) among males between the ages of 45 and 54 based on U.S. mortality rates from 1982,[13] which is approximately the average of the hypothetical population.

[D]Number of workers calculated by assuming each worker contributed 50 person-years to the study.

detecting the levels of risk that are of general concern to regulatory agencies and that need to be estimated in QRAs. Although rigid criteria for significant (deminimus) risk have not been established, the U.S. Environmental Protection Agency (EPA) and Food and Drug Administration have generally set regulations to limit risks to between 1 per 100,000 and 1 per 1,000,000. The Occupational Safety and Health Administration (OSHA) in its most recent rulings on carcinogens has generally adopted exposure limits that correspond to a lifetime risk of 1 per 1000 workers.

Estimates of the population size required for a retrospective, cohort, mortality study to have 80% statistical power[A] (at $\alpha = 0.05$) for detecting lung cancer risks corresponding to the levels of risk of between 1 per 100 and 1 per million are presented in Table I. These estimates were constructed for a hypothetical cohort of male workers who were followed for 50 years. In practice, the average period of follow-up in most occupational cohort mortality studies is considerably less than 50 years; thus, these estimates are most likely underestimates of the true sample sizes that would be required.

It is readily apparent from Table I that extremely large sample sizes would be needed to detect the levels of risk of concern to U.S. regulatory agencies. Even at the nominal deminimus risk level of 1 per 1000 (used by OSHA), a sample size of nearly 400,000 workers would be required. Few retrospective, cohort, mortality studies have been performed that have included this many workers, and thus, it is extremely unlikely that sufficiently large cohorts can be identified to detect risks below 1 per 1000. It is also noteworthy that few epidemiologists would be willing to accept relative risk estimates as low as those presented in Table I as being causally significant (even if it was statistically significant) because it is difficult to fully dismiss the potential for confounding at such low levels of relative risk.

Therefore, negative epidemiologic studies generally cannot be used to rule out the levels of risk that are of concern to regulatory agencies because of the limitations in statistical power discussed above. Negative epidemiologic studies, however, may still be useful for developing a likely upper bound (i.e., confidence interval) on the risk of exposure.

Meta-analysis, which involves the combination of study results, may be used to improve the sensitivity of epidemiologic studies.[15] However, combining occupational studies to perform a meta exposure–response analysis may be problematic because different methods are often used to estimate exposures in these studies.

Length of Follow-Up, Latency, and Lag Periods

Most regulatory agencies are interested in developing regulations based upon estimates of lifetime risks of exposures. This presents a problem for using occupational, cohort, mortality studies for QRA because, in most studies, only small segments of the population have been followed for an entire lifetime. In contrast, in most animal bioassay studies, the animals are observed for nearly their entire life span. Thus, some epidemiologic investigations may be negatively biased if the study population was simply not followed for a sufficiently long period of time.

The total time from first exposure to the clinical detection of or death from cancer has been termed the "empirical induction time" by Rothman[16] but is more frequently referred to as the time since first exposure (or imprecisely as the latency period). As illustrated in Figure 1, this period of time can be conceptually divided into two phases: 1) the time from first exposure to the development of a malignant cell termed the "induction period" and 2) the time from when a cell becomes cancerous until the clinical detection of the

[A]One minus the probability (β) of making a Type II error (failing to reject the null hypothesis when it is false).

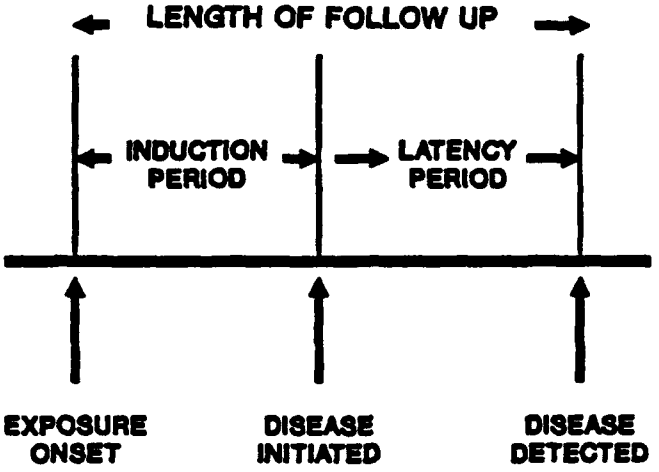

FIGURE 1. Length of follow-up.

tumor (or death from the malignancy) termed the "latency" or "lag" period.[16] Exposures that occur during the lag period may be expected to have no effect on tumor incidence and should be discounted from exposure–response analyses.

Although the actual lag period is generally unknown, it can be estimated empirically by iteratively refitting models with different assumptions about the length of the lag period.[17] The lag period that results in maximizing the goodness of fit of the model may then be chosen for use in the final risk assessment model.

Although the induction period generally cannot be measured in cohort mortality studies, the effect of the empirical induction time (i.e., time since first exposure) can be assessed. If the empirical induction period modifies the effect of exposure, then extrapolations for QRA need to take this into account.

Statistical Analyses

Model Selection

Risk assessors have long recognized the difficulty of selecting an appropriate mathematical model for extrapolation in QRA using animal bioassay data.[18] While it is possible to empirically choose models that describe the data well in the range of the observed data, the true dose–response relationship for the lower dose range is generally unknown and can only be inferred based upon biological and statistical considerations. This problem is generally not circumvented by using data from occupational mortality studies because these studies most often include individuals who were exposed to relatively high exposures in the past and, as demonstrated above, extrapolations beyond the range of the data are generally required for estimating low-dose risk owing to limitations in statistical power.

In the following sections, examples are drawn for heuristic purposes from an assessment recently performed by researchers at the National Institute for Occupational Safety and Health (NIOSH)[19] of the risk of lung cancer associated with cadmium exposure based on a NIOSH retrospective, cohort, mortality study of workers from a cadmium production facility.[20,21]

Statistical Models

Most QRAs based on occupational mortality studies have been based upon purely statistical models as opposed to biologically based models (described below). Considerable progress has been made in developing statistical methods for modeling hazard rates[B] from occupational, cohort, mortality studies in the past decade. An excellent review of these modeling techniques is presented in Breslow and Day.[22] These models may be broadly categorized into two classes: 1) models in which the effect of exposure adds to the background rate (additive models) and 2) models in which the effect of exposure multiplies the background rate (multiplicative models). These two classes of models may be represented mathematically as follows:

$$\text{additive: } \lambda(t) = \lambda_0(t) + r\{x(t)\beta\} \quad (1)$$

$$\text{multiplicative: } \lambda(t) = \lambda_0(t) r\{x(t)\beta\} \quad (2)$$

where: $\lambda(t)$ = predicted hazard rate
$\lambda_0(t)$ = background hazard rate at age t
$x(t)$ = vector of exposure and other explanatory variables
β = vector of regression parameters
$r\{x(t)\}$ = relative rate function (for Equation 2) or an excess (for Equation 1) rate function

Rate functions ($r\{x(t)\}$) that have been commonly used for models of cohort mortality data include:

$$\text{exponential: } r\{x(t)\beta\} = \exp(x(t)\beta) \quad (2a)$$

$$\text{additive relative rate: } r\{x(t)\beta\} = (1 + x(t)\beta) \quad (2b)$$

$$\text{power: } r\{x(t)\beta\} = (x(t) + k)^{\beta} \quad (2c)$$

where: k = small "background" exposure level, which is often assumed to be 1

The functional forms previously described may be fitted to data from occupational, cohort, mortality studies with person-years and observed deaths categorized by the exposure and other explanatory variables using Poisson regression.[23] Alternatively, with the exception of the additive model, all of these functional forms may be fitted to data from occupational, cohort, mortality studies by modeling the

[B] The hazard rate is the instantaneous probability of dying from the disease given survival prior to that time.

hazard rate continuously using the Cox proportionate hazards model.[24]

In theory, these two approaches should yield similar results assymptotically.[25] In practice, as the results presented in Figure 2 from the NIOSH cadmium risk assessment[19] illustrate, these regression methods may yield somewhat different results. The coefficient for cadmium exposure was approximately three times lower from the Cox proportional hazards model than from the Poisson regression model, even though both models had the same functional form (additive relative rate) and parameters.

In general, selection of an appropriate functional form for modeling cannot be based solely on statistical criteria of goodness of fit. Several models may provide a reasonable fit to the data, and it is generally necessary to consider additional information (e.g., biologic) for choosing an appropriate model for QRA. On the other hand, a model that does not fit the data in the observed data range is unlikely to be a reliable model for predicting low-dose risks.

An example of this dilemma is presented in Figure 3 from the NIOSH cadmium risk assessment.[19] In this assessment, the goodness of fit of the various functional forms described above was evaluated using Poisson regression. The power function, additive relative rate, and exponential multiplicative models all provided a reasonably good fit to the observed data, whereas the additive model did not appear to fit the data well. The power function model, which fit the data the best (i.e., lowest model deviance), was not chosen for the QRA

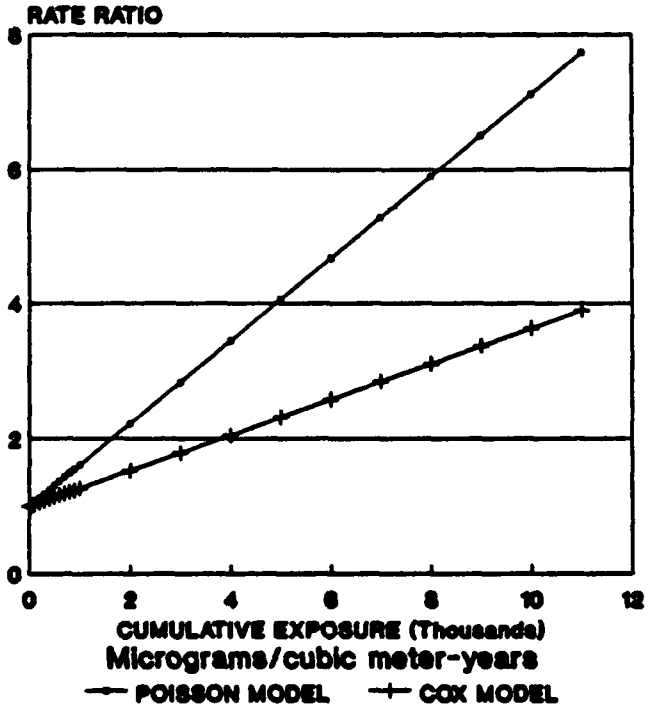

FIGURE 2. Comparison of rate ratio estimates from models of the NIOSH cadmium cohort study. Data lagged 5 years.

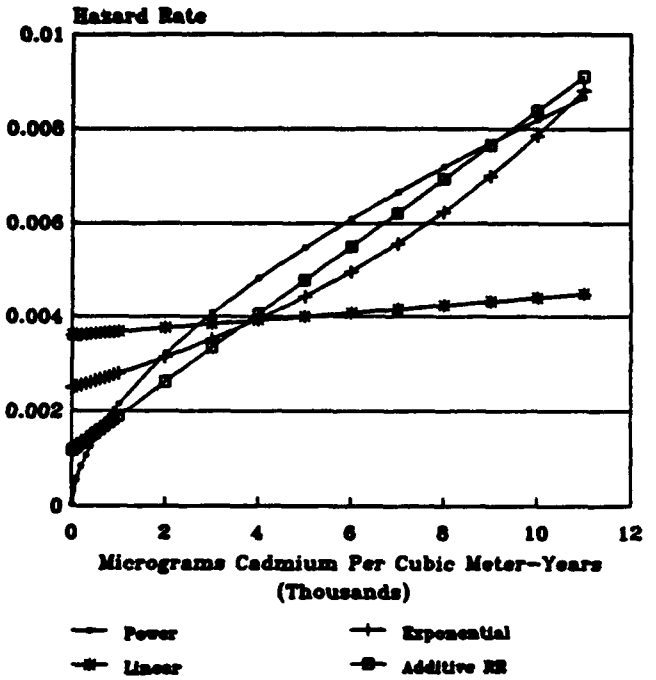

FIGURE 3. Poisson model hazard rates as a function of cumulative cadmium exposure based on lagged 5-year analysis for white males, age 70, 1940–1960.

because the model predicted background hazard rates that were nearly two orders of magnitude lower than the rates in the U.S. general population. The use of the power model for the QRA would have resulted in grossly inflated estimates of relative and excess risk. The additive relative rate model, which was the next best-fitting model, was chosen as the model for the QRA. It is noteworthy that the hazard rate estimates derived from these models diverge by over an order of magnitude at the extremes (i.e., high and low doses) of the exposure–response curves.

Internal versus External Analysis

Standardized mortality ratios (SMRs) are generally reported as the effect measure in most occupational cohort mortality studies. The SMR is the ratio of the number of deaths observed to the number expected and is frequently multiplied by 100 to express the ratio as a percentage. The expected number of deaths is calculated by applying the age-, calendar time-, race-, and sex-specific person-years distribution of the study population to the corresponding rates from an external referent group (e.g., the U.S. population).

Risk assessors have modeled SMRs that are reported in occupational, cohort, mortality studies for several exposure groups and, sometimes, even with just one group.[26] The models discussed above may be modified to incorporate external rates yielding the following mathematical forms that are analogous to Equations 1 and 2:

$$\text{additive: } \lambda(t) = \lambda^*(t) + r\{x(t)\beta\} \quad (3)$$

$$\text{multiplicative: } \lambda(t) = \lambda^*(t)r\{x(t)\beta\} \quad (4)$$

where $\lambda^*(t)$ represents the external mortality rates and the other parameters are unchanged from the Equations 1 and 2 described above. Equation 4 may also be expressed in terms of modeling the SMR using the following form:[25]

$$\frac{OBS}{EXP} = r\{x(t)\beta\} \quad (5)$$

where: OBS = observed
EXP = expected number of deaths

Although modeling SMRs may be the only possible approach if the risk assessor only has access to published tables, there are at least two serious potential problems with this approach. First, because SMRs are indirectly standardized, the SMRs from different exposure groups are not standardized to the same standard and, thus, are not directly comparable.[11] Therefore, the modeling of SMRs from several exposure groups may be biased by demographic (e.g., age, race, or sex) or other differences between the categories. Second, and probably of greater significance, is the well-known fact that SMRs may be negatively biased because of the "healthy worker effect";[27,28] i.e., a working cohort may have a lower incidence of disease (or mortality) than the general population (the referent) simply because they are healthy enough to be employed.

An alternative analytic approach, which avoids the pitfalls described above for the analyses of SMRs, is to base the analysis on internal comparisons within the cohort using the modeling techniques described above (i.e., Equations 1 and 2). Although most occupational cohort mortality studies do not include an internal nonexposed group, an internal analysis is still possible as long as there is a range of exposures within the cohort. The inclusion of an internal, nonexposed, referent group, when available, does add some stability to the regression model.

Figure 4 presents a comparison of the results from an analysis of the risk of lung cancer in relation to cumulative exposure to cadmium that was performed by OSHA[29] with the results from the NIOSH cadmium risk assessment[19] to illustrate the potential bias that may be introduced by the modeling of SMRs. Both analyses were performed on the findings of a NIOSH cohort mortality study of cadmium smelter workers,[20] although the NIOSH analysis was based on a more recent follow-up of this cohort.[21] OSHA also produced risk estimates based upon a multistage model of a rat bioassay study,[30] which are also presented in Figure 4 for comparison purposes.

For its analysis of the epidemiologic data, OSHA performed a Poisson regression of the SMRs reported by Thun et al.[20] using an additive relative rate function. The risks predicted from OSHA's epidemiologic risk assessment were approximately seven times lower than the risks predicted by modeling of the rat bioassay data. It was suspected that, at least in part, this discrepancy might be explained by the potential negative bias in the SMR analysis due to the healthy worker effect. In the NIOSH assessment, a similar functional form (i.e., additive relative rate) was fitted using Poisson regression, but the model was fitted to the internal stratum-specific rates generated directly from the study. It can be seen that the NIOSH risk estimates were higher than those from OSHA's epidemiologic assessment, but they were still somewhat lower than the estimates produced by the multistage modeling of the rat bioassay study. Thus, it appears that OSHA's reliance on modeling the SMRs, as opposed to internal analysis of the rates within the cohort, introduced a negative bias in the estimation of risks.

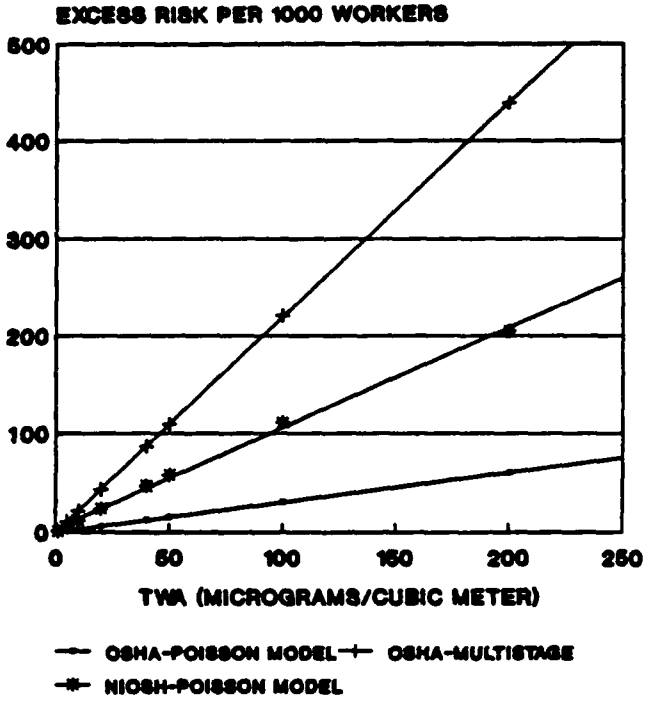

FIGURE 4. Comparison of NIOSH and OSHA excess risk estimates for cadmium exposure, assuming 45 years of exposure.

Biologic Models

Biologically based models, particularly models based on the multistage theory of carcinogenesis,[31] have often been used for producing risk estimates from animal bioassay data. These models have the advantage over statistical models of being based on biologic theory, thus providing a theoretical basis for extrapolation to low doses. On the other hand, these models may be oversimplified representations of the complex processes involved in carcinogenicity, and the validity of these models warrants further investigation.

The multistage theory suggests that, in order for a cell to become cancerous, it must progress through a series of ordered, independent, and irreversible stages. Stochastic models have been derived based on the multistage theory for

application to animal bioassay data. The quantal multistage model[32] has been the most commonly used model, which is fitted to the proportions of tumors at the end of the experiment using the following mathematical functional form:

$$P = 1 - \exp(-(q_0 + q_1 d + \ldots + q_k d^k)) \quad (6)$$

where: P = cumulative risk
q = regression coefficients
d = dose
k = number of stages affected by the exposure

A "linearized" version of Equation 6, based on the upper 95% confidence limit on the linear parameter (q_1) has been used extensively by EPA for its QRAs.[33] A time-to-tumor version of the multistage model has also been developed for modeling the time to the event (tumor) in animal bioassay studies.[34]

The multistage model has been shown to provide a reasonable description of the relationship between cancer incidence and age[31] for most nonhormonally mediated cancers in humans. Doll[35] has reported that the effect of cigarette smoking on lung cancer risk appears to be consistent with smoking altering the first parameters stage of a five-stage model, whereas other analyses indicate that smoking may act on both the first and fourth stages.[22] The multistage model has only been applied in a few cases to the analysis of occupational, cohort, mortality data.[36,37]

The implications of the multistage model may be explored indirectly by examining how the patterns of relative (or excess) risk in an epidemiologic study are modified by age at initial exposure and time since last exposure.[38] If a carcinogen acts on the first stage of the process, then 1) relative and excess risk are increasing functions of time since last exposure and 2) excess risk is independent of age at initial exposure, whereas the relative risk decreases with increasing age at initial exposure. If a carcinogen acts on the penultimate (next to last) stage of the process, then 1) relative and excess risk increase with age at initial exposure and 2) the excess risk is independent of time since last exposure, whereas the relative risk decreases with increasing time since last exposure. For example, in a NIOSH[39] assessment of radon daughters and lung cancer risk, the relative risk was observed to increase with age at initial exposure and decrease with time since last exposure, suggesting that radon acts on a late stage in the carcinogenic process.

Recently, two-stage models of carcinogenesis have been proposed for use in risk assessment.[40] In addition to allowing for two mutational events, these models allow for the influence of exposures on cell growth and differentiation. Two-stage models have been shown to provide a reasonable description of the age incidence curves for most human tumors, including hormonally mediated tumors that are not well described by the multistage model.[41] These models have not as of yet been applied to QRA for occupational or environmental exposures.

Translating Rates to Risks — Extrapolation Models

As mentioned earlier, regulatory agencies generally require estimates of lifetime risk for their decision-making process. Thus, the hazard rates (or rate ratios) that are estimable from the statistical models described in this paper need to be converted to estimates of lifetime risk. In order to make this conversion, assumptions need to be made about the duration and timing of the exposure. For occupational QRAs, it has generally been assumed that the workers are exposed for approximately 45 years (i.e., a working lifetime) starting at age 20, whereas for environmental QRAs, the exposure has generally been assumed to be initiated at birth and to last until death at approximately 70 years of age.

Gail[41] has proposed methods for computing lifetime risk based on actuarial methods, which account for the effects of competing causes of death. For multiplicative models, the lifetime risks of occupational exposures may be estimated using Gail's method to estimate the risks of 45 years of exposure at age 75 based on the following formula:

$$\sum_{i=20}^{74} (RR_i - 1)\, q_d(i) \exp\left[-\sum_{j=20}^{i} \{(RR_j - 1)\, q_d(j) + q_a(j)\}\right] \quad (7)$$

where: RR_i = rate ratio estimate from the model for exposure achieved at age i
$q_d(i)$ = background age-specific rate for the disease of interest
$q_a(i)$ = background age-specific mortality for all causes
i = age indices

The results from the application of this approach to the estimation of lifetime risks from occupational exposure to cadmium based on the additive relative rate models from the NIOSH[19] QRA are presented in Table II. Based on this assessment, the lifetime risk of dying from lung cancer after 45 years of exposure at the current OSHA standard for cadmium fumes of 100 $\mu g/m^3$ was estimated to range from 5 to 10 per 100 workers. Note that in this model (Equation 7), the rate ratio is assumed to be constant with age at risk and length of follow-up and is solely dependent on the exposure achieved (at age i). Adjustments to the extrapolation model need to be made if there is evidence that the effect of exposure is modified by these or other covariates.

Conclusion

The purpose of this paper was to review and discuss the major methodologic issues related to the use of epidemiologic data for risk assessment. Although animal studies have been most often used for QRA, it is generally recognized that well-conducted epidemiologic studies would provide the best basis for estimating human risk. However, the observational

TABLE II. Estimates of Excess Risk per 1000 Workers Based on the Poisson Regression and Cox Proportional Hazards Additive Relative Rate Models in the NIOSH Cadmium Risk Assessment*

TWA ($\mu g/m^3$)	Excess Risk Estimates (per thousand workers)	
	Poisson Model	Cox Model
1	1.2	0.5
5	6.0	2.6
10	11.9	5.2
20	23.7	10.3
50	57.7	25.4
100	110.9	49.9
200	205.2	96.4

*Risk estimates are based on the results from the 5-year lagged analysis.

nature of epidemiologic studies often introduces several sources of uncertainty that are generally not present in QRAs based on animal experiments.

The lack of adequate exposure (or dose) information is the most frequently cited reason for not using epidemiologic data for QRA. There is reason to hope that, in the future, improvements will be made in the estimation of exposure in epidemiologic studies and that biologic markers and pharmacokinetic models will be used to estimate target tissue doses. Other aspects of epidemiologic study design, e.g., confounding, effect modification, length of follow-up, and statistical power, may also limit the usefulness of epidemiologic data for QRA. Even if these limitations can be overcome, as with animal studies, substantial uncertainties exist as to the choice of a proper statistical (or biologic) model for extrapolation from epidemiologic results.

Because of the limitations discussed in this paper, epidemiologic data should not be viewed as a panacea for the problems inherent in using animal bioassay data for QRA. This is not to belittle the importance of epidemiologic data. On the contrary, epidemiologic data is of vital importance to QRA and hopefully will play an even greater role in the future. The information that can be derived from epidemiologic and toxicologic studies complement one another, and both data sources need to be used to provide the best characterization of human risk.

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Exposure Assessment in Risk Assessment

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The assessment of exposure is an important component of the risk assessment process. Exposure information is used in risk assessment in at least two ways: 1) in the identification of hazards and the epidemiologic research investigating exposure–response relationships and 2) in the development of population exposure estimates. In both of these cases, the value of a chemical risk assessment is enhanced by improvements in the quality of exposure assessments. The optimum exposure assessment is the direct measurement of population exposure; however, such measurements are rarely available. Recent developments in methods for exposure assessment allow estimates to be made that are valid representations of actual exposure. The use of these exposure estimates to classify exposures correctly enhances the likelihood that causal associations between exposure and response will be correctly identified and that population risks will be accurately assessed.

Introduction

Chemical risk assessment is founded upon the premise that exposure causes risk. The presence of exposure indicates potential risk. In the simplest case, for example, those without exposure are subject to some background level of risk of an adverse health outcome, whereas those who are exposed may experience some increment of risk above background. The quantitative risk assessment seeks to describe the nature of the association between exposure and the response which constitutes the additional risk.

Exposure assessment is an important component of the overall risk assessment process. The information derived from exposure assessment may be used at two points, at least, in quantitative risk assessment. The first is in research, particularly in the human epidemiologic studies that are important for hazard identification and the assessment of exposure/dose–response associations.[1] In these studies, valid exposure assessment is essential to identify these associations and to establish evidence that the associations are causal in nature. The criteria that are applied to evaluate the likelihood of a causal association (e.g., the strength of the exposure–response association, the presence of an exposure–response trend, and a clear temporal relationship between exposure and development of the effect) all require at least an indirect assessment of exposure.[2]

The second use of exposure information is as a classification variable when risk assessment models are used to estimate population risks. In this case, exposure status is an independent variable used in a predictive model to estimate population risks, so error in exposure assessment will result in error and uncertainty in the risk estimates. The quality and predictive value of quantitative risk assessments are enhanced, therefore, by improvements in the assessment of exposure.

The Exposure/Dose–Response Continuum

The discussion of exposure assessment in quantitative risk assessment can begin by examining the concept of exposure itself. Particularly for the case of environmental contact with chemicals, exposure can be viewed as part of a process through which a chemical produces a toxic response or health effect. When the chemical is, in fact, the cause of the observed effect, the pathway from source to response may be termed a causal continuum. As shown in Figure 1, there are several components of this pathway, of which exposure is one.

Ambient Concentration

The pathway starts at the source of the chemical itself. For our purposes, the source may be considered to be the point of release of the chemical into the environment. The source may be a stack releasing sulfur dioxide (SO_2) into the atmosphere, an outfall from a sewage treatment facility, a furnace in a foundry, or a new carpet in an office building. When a source has released a chemical, the chemical's presence in the environment is characterized as an ambient concentration. It may be described in units such as mass per volume, e.g., milligrams of particulate material per cubic meter of air (mg/m^3) or micrograms of chloroform per liter of drinking water ($\mu g/L$). All measures of ambient concentration are defined in such terms of units of the contaminant per unit of the environmental matrix.

Exposure

The ambient concentration is an environmental measure, which is independent of any human interaction. When people come into contact with a chemical through an environmental medium, the process is termed exposure. The factor that distinguishes between ambient concentration and exposure is

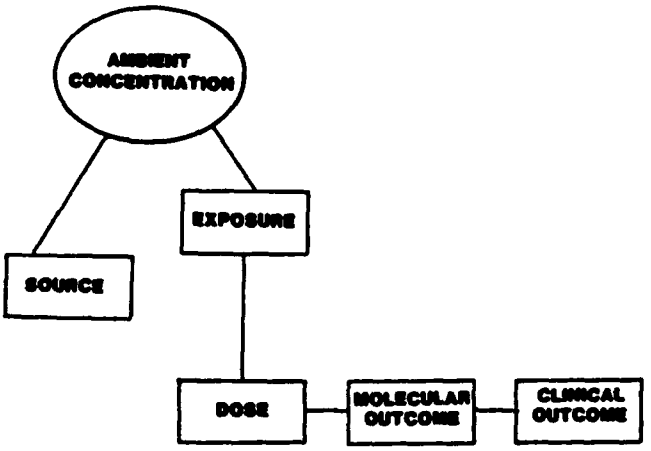

FIGURE 1. Conceptual model of causal association in occupational epidemiology.

the human interaction with the environment. Just as a tree falling in the forest may release energy in the form of sound waves, it is noise only if there is someone there to hear it. By the same logic, the presence of a contaminant in an environment does not necessarily constitute exposure, unless there is a receptor in the environment to come into contact with the contaminant. Exposure is the result of human contact with an ambient concentration of a chemical. Following the causal pathway in Figure 1, we reach the center concept of exposure resulting from human interaction with the environment.

When exposure is considered as a component of the causal continuum, it is helpful to think of it in terms of a process, rather than an event. Although there are momentary events and short-term exposures that may cause adverse health effects, most risk assessments should consider exposure to be a process occurring over time. Exposure can then be regarded as a dynamic process in three dimensions: composition, magnitude, and time.

Composition of Exposure

Accurate exposure assessment requires a complete understanding of the composition of exposure. If we are to correctly identify associations between exposure and effect, the true composition of the exposure must be known. In epidemiologic studies, the incomplete or inaccurate assessment of the composition of exposure may result in the failure to identify a causal association between exposure and response, or erroneous attribution of cause through confounding or effect modification. In a recent study of exposure to the industrial chemical 1,3-butadiene, we discovered that the analytical method which had been used historically to measure exposures to this chemical may have incorrectly included measurements of compounds other than butadiene along with the actual butadiene exposure. The source of this uncertainty was the incomplete resolution of these compounds in the gas chromatographic analysis.[3] The result of this lack of analytical specificity could be overreporting of the true butadiene exposure, which would result in errors in describing the exposure–response relationship if this exposure data were used in a quantitative risk assessment. Another example of the importance of knowing the composition of exposure comes from animal studies of SO_2 exposure and aerosols. Atmospheric particles smaller than 1 μm in diameter were found to strongly potentiate the irritant effect of SO_2 compared with exposure to gaseous SO_2 alone or in combination with large-diameter particulate material.[4] If the true composition of these mixed atmospheres were not known, including the gaseous SO_2 and the aerosol size distribution, the actual exposure–response relationship between SO_2 and pulmonary irritation would be obscured.

Magnitude of Exposure

Another characteristic of exposure that must be assessed is its magnitude. The accurate quantitation of the level of exposure is an essential component in the assessment of risk. Methods to measure the level of exposure are the subject of several full disciplines spanning methods derived from air pollution, industrial hygiene, and a range of occupational and environmental health sciences. The methods for assessment of chemical exposures are usually driven by, and limited by, the laboratory practice of analytical chemistry. The measurements made using these methods usually reflect what is possible analytically rather than what may be the best information for studying the association of the exposures and health effects. For example, painters using epoxy-based coatings may be exposed to aerosols containing epoxy resin molecules which have two functional epoxy groups each. These reactive epoxy groups are responsible for a range of toxic effects associated with epoxy resins, such as sensitization and mutagenesis.[5] Epoxy paints are prepared for application by mixing the resin with a curing agent that reacts with the epoxy groups. The mixture that constitutes the painters' exposure contains some epoxy resin molecules which have begun to react with the curing agents in the mixture, forming polymeric chains. These chains still contain available (unreacted) epoxy functional groups, however, and a measurement method that is sensitive only to the unreacted DGBA molecule can seriously underestimate the effective total epoxy exposure.[6] Limitations such as these may become apparent when we consider exposure as it is related to dose as a cause of effects in biological systems.

Exposure Over Time

The third dimension that can be applied to exposure is time. Exposure is a process occurring over time, and the first two characteristics (composition and magnitude) change over time. Accurate assessment of exposure must recognize the dynamic nature of exposure over time and consider the effect of these changes on the nature of the exposure–response

relationship. Monitoring techniques available today, for example, allow continuous monitoring of chemical exposures in real time. In studies such as an investigation of the association between ozone levels and respiratory function in children, continuous monitoring for ozone revealed that the concentration in the hour preceding pulmonary function testing was the strongest predictor of effect as compared with exposure levels averaged over other time intervals, as well as cumulative exposure.[7] In chronic diseases such as cancer, cumulative lifetime exposure to compounds such as asbestos and benzene have been strongly associated with disease risk.[8,9] In these studies of chronic effects, exposure levels changed dramatically over the time during which the study subjects were exposed. Exposure assessment to document the changes in the level of exposure over time was essential in developing accurate exposure estimates to correctly classify study subjects in the epidemiologic analysis.

The time at which a subject's exposure occurred can be important in investigations of the exposure/dose–response process. The age of an individual at the time of exposure, or during the period over which exposure occurs, is a factor which could influence the likelihood that exposure will result in a health effect. It is known from animal studies, for example, that younger animals are more susceptible to the induction of cancer from exposure to polycyclic aromatic hydrocarbons than are older animals.[10] Therefore, age at the time of exposure should be considered as a variable in evaluating these associations. The time sequence of exposures may also be a determinant to be considered in an exposure assessment. If exposure to an agent that is a promoter of a carcinogenic response takes place after an initiating event, the eventual health outcome could be very different than if the order of exposure were reversed. An exposure assessment that identified the occurrence of both exposures without noting their time sequence could obscure the actual association between exposure and risk.

Dose

In our efforts to improve the quality of exposure assessment, it is important to recognize that exposure itself is not the proximate cause of a biological change or a health effect. Exposure is a process that results from human interaction with an ambient concentration of a contaminant. The assessment of exposure is an environmental measurement; we need to recognize that exposure is not the same as dose, although they are closely related. As shown in Figure 1, exposure and dose are related parts of the causal continuum, but there are important differences between the two. For our uses, dose can be considered to be a measure of an agent at a receptor site in a living system.[11] The molecular site at which biochemical events take place is not accessible for direct measurement. Although we do not have the ability to directly measure the quantity of a toxin directly at its point of action, we can make a measure of exposure that is representative of and correlated with dose. In this manner, we can determine exposure as the environmental precursor of dose. Using this as our operational definition, we can refine our methods of exposure assessment to optimize the value of exposure as a dose measure.

In studies that seek to evaluate the association between exposure and effect, exposure should be assessed as the best possible surrogate or marker of dose. This means that exposure measures must consider factors that will mediate the pathway between exposure and dose (e.g., the characteristics of exposure itself such as composition and magnitude over time) and the characteristics of the exposed population. Factors such as the age and gender distribution of an exposed population can have a very significant effect on the relationship between the exposure and the dose to critical biological units between individuals in the exposed population. Occupational factors, such as contact with other chemicals on the job, can have a significant impact on the nature of an exposure–response association, e.g., the synergistic effect of polycyclic aromatic hydrocarbons and sunlight in the risk of photosensitization and skin cancer among roofers and highway construction workers.[12] Factors related to lifestyle and personal behavior can have a substantial impact on exposure–response associations, as in the case of smoking among asbestos–exposed workers. Exposure assessment must be comprehensive in approach, recognizing the characteristics of the exposure of primary interest, of other potentially confounding exposures, and the characteristics of the exposed populations that will influence the association between exposure/dose and response. When exposure assessments are optimized to identify exposure correctly and to classify study subjects based upon exposures that are relevant to the effect being observed, the power of study to identify an association and to establish evidence that it is causal in nature is enhanced.

Exposures of Populations

In hazard identification and epidemiologic research, or in risk estimation, the quality of the exposure information is an important determinant of the quality of the risk assessment. When a causal relationship between exposure/dose and response has been identified, or when evidence for such an association is being evaluated, assessment of exposure as a valid indicator or surrogate of dose is essential. The goal of an exposure assessment, therefore, is to provide an accurate exposure value for each member of the population of interest. One approach to obtain this is to assess exposure by direct measurement for each individual in the population. This has been done in some well-defined populations, usually in occupational settings, when the outcome of interest is an effect with a short period of induction or latency, such as a level of enzyme activity or a molecular end point. Studies such as these can be conducted cross-sectionally allowing individual exposure and effect measurement for each study subject.

This can be a powerful approach to research and risk assessment because exposure measurement techniques can be used that continuously monitor the level and pattern of personal exposure over time.[13] In most situations, this sort of direct measurement is not possible, and some method for estimating exposures from limited information must be employed.

The simplest exposure assessment for a population is the dichotomous classification into exposed and unexposed groups. Members of the population of interest can be classified on the basis of ever having been in a situation of potential exposure to the contaminant(s) of interest. Examples of such dichotomous classification could be 1) ever having lived with a smoker (yes or no), 2) ever having worked in a chemical production facility, or 3) ever having lived in an area served by a particular municipal water supply system. A simple classification system such as this offers the advantage that it is likely to distinguish individuals between the two categories correctly. There are a number of disadvantages to such a system. Specifically, it is qualitative in nature, providing very little information about the nature and magnitude of exposure. By using such a surrogate measure of exposure, the amount of misclassification may be low, but the value of the exposure classification for risk assessment is limited. However, this sort of classification has been useful in investigating associations between employment in particular industries and disease, e.g., studies of cancer of the respiratory tract among coke oven workers.[14]

A variety of exposure assessment methods may be considered as semiquantitative approaches. These techniques are an improvement over the simple, dichotomous classification because they attempt to classify members of a population based upon the magnitude of exposure on a relative scale. A common assessment technique is to use duration of exposure as a marker for total, cumulative exposure. The extent to which total length or duration of exposure accurately represents total exposure is limited by the homogeneity of exposure level between members of the study population, as well as over time. If all members of the population have the same level of exposure and if that level is constant over time, then a ranking of population members by total duration of exposure would be identical to ranking by cumulative exposure. These conditions of constant, homogeneous exposure over time are rarely met, however, and the use of duration of exposure as an exposure assessment outcome can result in substantial misclassification.[15] In cases where information has been available to examine both duration of exposure and some other exposure classifier which accounted for differences in exposure between individuals and over time, duration has been found to be an inferior predictor of risk.[8,9]

In recognition of the variability in exposure between individuals and over time, exposure assessment strategies have been developed employing ordinal ranking systems to classify individuals into categories based upon level of exposure. These approaches are frequently used when a limited amount of measured exposure information is available. In such cases, an exposure value measured for a portion of the study population may be assigned to others in the population who are considered to be similar in terms of factors that determine their exposure. This approach offers the advantage of allowing examination of the nature and shape of the exposure/dose–response relationship, as the exposure classes have a numerical value associated with each of them. The major disadvantage of this approach is that errors in the assignment of individuals to the classes and errors in the ranking values used for the classes tend to create exposure misclassification which dampens the apparent relationship between exposure and response, provided the classification errors are random.[16,17]

The most quantitative approach to exposure assessment (short of making individual personal exposure measurements) is to develop a strategy to assign unique exposure values for each member of the study population over the period of interest. This approach has been employed when there is at least some measured exposure information that will support the development of a predictive model to estimate exposures for individuals and time periods where measured exposures are not available. The available information on the levels of exposure and the characteristics of the members of the study population can be used to develop statistical models that predict exposures. Although this approach to exposure assessment requires sufficient measured data to support the development of a predictive model, it has the advantage of generating point estimates of exposure that can be used for quantitative risk assessment.[8,18]

Exposure Misclassification

If we consider exposure as a risk factor for the development of a health effect or disease, the nature of an association between risk and effect can be fully and correctly evaluated only when the risk and effect measures are valid. Incorrect assessment of either exposure or effect results in misclassification that can obscure true associations and lead to error or uncertainty in risk assessment.

Exposure misclassification is most likely to be nondifferential in nature; that is, errors in exposure classification will occur throughout the study population, without regard to health or outcome status. In the simplest case, members of a study population who are truly exposed may be incorrectly classified as unexposed, and some exposed are classified as unexposed. In this case, the net result will be a bias in the study findings toward the null hypothesis of no association between exposure and response. In more quantitative exposure assessments, such as the assignment of individuals to rank-ordered categories based upon cumulative lifetime exposure, nondifferential misclassification between adjacent exposure categories can have an attenuating effect on an exposure–response trend, if one, in fact, exists.[19] Even when

the exposure misclassification rate is only 20%, the true estimate of risk among the exposed can be substantially greater than the apparent relative risk. This holds whether the misclassification is between a simple exposed/unexposed dichotomy or by some more-quantitative exposure classes. A misclassification rate of 20% would not be at all surprising in epidemiologic studies, particularly when exposures must be estimated based upon a historical reconstruction for some members of a study population. In the few studies where estimates of historical exposures were compared with actual measurements of exposure from the past, agreement within 20% between estimates and measurements of past exposure would be considered very good. In many cases, much larger differences have been observed.[20]

Summary and Conclusions

Valid exposure assessment is an essential part of quantitative risk assessment. The incorporation of exposure information in hazard identification and research enhances the likelihood that these activities will correctly identify etiologic associations between exposure and response and accurately determine the strength of these associations. When a quantitative risk assessment is conducted to estimate population risks, accurate assessment of exposure will improve the validity of the risk estimates. Direct measurements of human exposures would be the most accurate assessment of exposure. Although such measurements are frequently not available, new approaches to exposure assessment are being developed to provide accurate exposure estimates for populations. These improvements in exposure assessment methodology offer the prospect for advances in the practice of quantitative risk assessment.

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Quantitative and Qualitative Extrapolation of Carcinogenesis Between Species

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As currently conducted, standard rodent bioassays do not provide sufficient information to assess carcinogenic risk to humans at doses thousands of times below the maximum tolerated dose. Recent analyses indicate that measures of carcinogenic potency from these tests are restricted to a narrow range about the maximum tolerated dose and that information on shape of the dose–response is limited in experiments with only two doses and a control. Extrapolation from high to low doses should be based on an understanding of the mechanisms of carcinogenesis. We have postulated that administration of the maximum tolerated dose can increase mitogenesis which, in turn, increases rates of mutagenesis and, thus, carcinogenesis. The animal data are consistent with this mechanism, because about half of all chemicals tested are indeed rodent carcinogens, and about 40% of the positives are not detectably mutagenic. Thus, at low doses where cell killing does not occur, the hazards to humans of rodent carcinogens may be much lower than commonly assumed. In contrast, for high-dose exposures in the workplace, assessment of hazard requires comparatively little extrapolation. Nevertheless, permitted workplace exposures are sometimes close to the tumorigenic dose–rate in animal tests.

Regulatory policy to prevent human cancer has primarily addressed synthetic chemicals, yet similar proportions of natural chemicals and synthetic chemicals test positive in rodent studies as expected from an understanding of toxicological defenses, and the vast proportion of human exposures are to natural chemicals. Thus, human exposures to rodent carcinogens are common. The natural chemicals are the control to evaluate regulatory strategies, and the possible hazards from synthetic chemicals should be compared to the possible hazards from natural chemicals.

Qualitative extrapolation of the carcinogenic response between species has been investigated by comparing two closely related species: rats and mice. Overall predictive values provide moderate confidence in interspecies extrapolation; however, knowing that a chemical is positive at any site in one species gives only about a 50% chance that it will be positive at the same site in the other species.

Introduction

Current strategies to prevent human cancer use chronic rodent bioassays as the major source of information to predict the risk to humans from chemical exposures. Two types of extrapolation are required in such an undertaking: 1) a quantitative extrapolation is necessary from the maximum tolerated dose (MTD) administered in bioassays to human exposure levels that are usually hundreds of thousands of times lower and 2) a qualitative extrapolation is necessary between a short-lived species, such as rats or mice, to humans, a long-lived species. This paper addresses a variety of issues relevant to these two types of extrapolation. We discuss why standard rodent bioassays, as currently conducted, do not provide sufficient information to assess carcinogenic risk to humans at low doses. Such extrapolation should be based on knowledge of mechanisms of carcinogenesis and should reflect the importance of mitogenesis. We have postulated that chronic administration of chemicals at the MTD increases mitogenesis in cells that are not discarded which, in turn, increases rates of mutagenesis and carcinogenesis.[1–3] Therefore, at the low doses of most human exposures where cell killing does not occur, the hazards to humans of rodent carcinogens may often be much lower than has commonly been assumed.

Results from rodent bioassays are often used to predict qualitatively whether a chemical is a potential human carcinogen. Ideally, one would like to know the accuracy of prediction from rats or mice to humans, but because epidemiologic data are usually lacking and experiments cannot be conducted in humans, this knowledge is not available. The accuracy of prediction between the two closely related species, rats and mice is examined below. These data reflect results obtained under similar experimental conditions, including administration of estimated MTDs and laboratory diets fed *ad libitum*. Thus, qualitative prediction from one rodent species to another (i.e., prediction of positivity and prediction of target organ) can be examined without simultaneously having to address the issue of high to low dose extrapolation.[4,5] One would expect that the qualitative prediction of positivity and target organ from rats to mice would likely be much better than prediction from rats or mice to humans. The quantitative prediction from high dose in rodents to low dose in humans is much more uncertain.

Quantitative Extrapolation to Low Dose from Bioassays Conducted at High Dose

Limitations of Carcinogenesis Bioassay Data for Risk Estimation

Several recent analyses indicate that measures of carcinogenic potency estimated from standard rodent bioassays are restricted to a narrow range about the maximum dose tested for each chemical.[6–9] This narrow range contrasts with the 10 million-fold range in the test doses (MTDs) of different chemicals. In our comprehensive, standardized database of chronic, long-term bioassays, the Carcinogenic Potency Database (CPDB), we use TD_{50} based on the one-hit model as the measure of potency (i.e., the tumorigenic dose rate for 50% of the animals at the end of a standard lifespan).[10–15] One reason for choosing the TD_{50} was that the concept is easily understood, particularly by analogy to the widely reported LD_{50}. Importantly, the TD_{50} is often within the range of doses tested; thus, the experimental results do not have to be extrapolated far to estimate TD_{50}. The statistical methods used to estimate TD_{50} do not matter greatly. There is substantial agreement between TD_{50} estimated by lifetable and summary analyses.[16] Additionally, among chemicals that are positive in more than one test in a species, the single, most potent TD_{50} value from among all positive tests in the species is, with few exceptions, similar to other measures that average TD_{50} values (harmonic mean, geometric mean, or arithmetic mean).[17]

Several years ago, we showed that the potency (TD_{50}) calculated from bioassays, as currently conducted, is constrained to be within a narrow range (~32-fold) about the maximum dose tested (in the absence of 100% tumors in all dosed animals).[6] Several papers that appeared later all confirmed this restriction.[18–20] Recently, Krewski, et al.[21] showed that across chemicals, regardless of whether one uses the one-stage, multistage, or Weibull model to estimate TD_{50}, the correlation between the MTD and carcinogenic potency is greater than 0.9. Thus, potency estimates are constrained to a limited range when one knows the MTD.

TD_{50} does not provide information about low-dose exposures. Thus, we have not attempted to say anything about the doses estimated to give tumors to one rat in a million. In contrast to TD_{50}, vastly different results would be obtained for such an undertaking, depending on what particular statistical model was fitted.[22] Whereas TD_{50} is close to the doses tested, an estimate of the dose to give tumors to a maximum of one animal in a million based on the linearized, multistage model widely used for regulatory purposes, averages 380,000 times below the bioassay high dose.[8] This enormous toxicological "leap in the dark" emphasizes the point that carcinogenesis bioassays were not designed to determine one-in-a-million risks.

A further limitation of bioassay data for quantitative extrapolation to low dose is the minimal information available about dose–response from an experiment with only two doses and a control. Even at the two high doses tested (MTD and 1/2 MTD), it is difficult to interpret the shape of the dose–response curve with three data points. A recent study[23] tested for consistency of the dose–response with three different curves: linear, square-root, and quadratic. Results of bioassays from the National Cancer Institute/National Toxicology Program (NCI/NTP) indicate that two-thirds of the curves are consistent with all three models, and 83% are consistent with at least two models. More of the best fits are consistent with a quadratic model than either a linear or square-root model. An additional complication is the finding that the best fit curves for more than half the chemicals are not the same for different sex-species groups or different target organs within a single experiment. This variation in curves for the same chemical was also discussed earlier.[6,16]

The good correlation in carcinogenic potency between rats and mice at the high doses tested has been interpreted as a justification for quantitative extrapolation from rodents to humans. However, the MTDs of rats and mice for different chemicals are also very highly correlated; as previously stated, they span a 10-million-fold range across chemicals, whereas the potency for a given chemical is constrained to a narrow range about the MTD.[6] These facts imply statistically that the potencies of chemicals positive in rats and mice will be highly correlated. Thus, the study of potency correlations between rats and mice does not shed much light on the issue of quantitative prediction between species. The biological basis for these correlations lies, in part, in the high correlation in the MTDs of the two species and, in part, in the experimental finding that it is uncommon to observe either a plateau in the dose–response curve or a tumor incidence of 100% in experiments conducted using the standard bioassay design. These results are consistent with the hypothesis that mitogenesis induced by the near toxic doses administered is important in the carcinogenic response. The limitations of bioassay data for use in risk estimation underscore the importance of understanding mechanisms of carcinogenesis.

Several recent analyses have shown that quantitative risk assessments as currently conducted by regulatory agencies are also constrained to a narrow range about the MTD. Using data from the CPDB, Krewski et al.[9,21] have shown that the unit risk factor Q_1^* derived from the linearized, multistage model is restricted to a limited range about the MTD, that empirically the Q_1^* values for different chemicals are highly correlated with the MTD, and that linear extrapolation from the TD_{50} usually results in low-dose slope estimates that are similar to those based on the linearized, multistage model. Gaylor[8] estimated the risk specific dose (RSD) corresponding to a maximum risk of one cancer in a million based on the multistage model and found that RSD averages 380,000 times below the MTD and that 90% of the estimates are within a factor of 10 of that number.

These are striking findings with broad implications for

risk assessment: the dose usually estimated by regulatory agencies to give a maximum of one cancer in a million can be approximated merely by knowing the MTD, and a reasonable estimate of the Q_1^* can be made from the TD_{50} values in our published CPDB. Proposals based on these findings have been made to facilitate the regulatory process. Although these proposals address the question of facilitating regulation as it is currently done, they do not resolve the fundamental question of the vast biological uncertainties in extrapolating 380,000 times below the bioassay dose. Rather, they assume that the current methodology should be approximated.

Gaylor[8] has proposed dividing the MTD by 400,000 to estimate the virtually safe dose; then, if the intended human exposure to a chemical is greater than the lowest virtually safe dose, the chemical cannot be accepted as safe. If the intended human exposure is below the lowest virtually safe dose, then conducting a bioassay may not be necessary because the predicted maximum risk will be below one in a million at the intended exposure level.[8] Rulis[24] proposed a threshold of regulation for safety assessment of packaging materials based on the distribution of TD_{50} values in the CPDB. This requires assuming that a substance is no more toxic than the most potent chemical carcinogen and inferring a theoretical upper bound on potency below which risks would be trivial. The California Department of Health Services has proposed that regulations for Proposition 65 be expedited by using the adjusted TD_{50} values for those chemicals that do not yet have a Q_1^* from either their agency or the U.S. Environmental Protection Agency (EPA). Zeise[25] has shown that potency estimates derived from TD_{50} are reasonable estimates of potency values proposed for Proposition 65.

Ranking Possible Carcinogenic Hazards

Our approach has been to acknowledge the enormous limitations and uncertainties in quantitative risk assessment and to begin by ranking possible carcinogenic hazards to humans from typical exposures for a wide variety of chemicals.[26,27] This ranking can help to set priorities when selecting chemicals for chronic bioassay or mechanistic studies, for epidemiological research, and for regulatory policy. The current regulatory process needs to take into account several points that we have previously discussed in detail:[1–3,26–29]

1. An extrapolation from high to low doses should be based on an understanding of the mechanisms of carcinogenesis.
2. Testing at the MTD can frequently cause chronic cell killing and consequent cell replacement, a risk factor for cancer that can be limited to high doses. Ignoring this mitogenesis effect can greatly exaggerate many low-dose risks.
3. About half of the chemicals tested at the MTD are positive, and about 40% of the positives are not mutagenic. This would be expected if mitogenesis is important in the carcinogenic response at the MTD.
4. About half of the *natural* chemicals tested chronically in rats and mice at the MTD are positive, and the natural world of chemicals makes up the vast proportion of chemicals to which humans are exposed. Thus, human exposures to rodent carcinogens (as defined by testing at the MTD) are likely to be common.
5. The toxicology of synthetic and natural toxins is not fundamentally different.

Together, these five points indicate that cancer–prevention strategies aimed at chemical carcinogens as potential causes of human cancer need to take a broad overview of chemical exposures to put possible hazards into perspective and to focus on those exposures that rank highest in possible hazard. If there is an enormous natural background of "potential human carcinogens" as defined by rodent tests, then smaller exposures to synthetic chemicals are not likely to be significant causes of human cancer. Ames et al.[28] have recently shown, for example, that even though only 52 of the 5000 or more naturally-occurring plant pesticides in our diet have been tested, the 27 that are rodent carcinogens are present in many common foods and at concentrations that are commonly thousands of times higher than the concentrations of synthetic pesticide residues. It is probable that almost every fruit and vegetable in the supermarket contain plant pesticides that are rodent carcinogens. A chemical pollutant should not be a high priority for concern with respect to carcinogenicity if its possible hazard seems far below that of many common food items.[28] This is not to say that these dietary exposures are necessarily of much relevance to human cancer; rather the background of exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens.

Our ranking of possible carcinogenic hazards is based on a simple measure, Human Exposure/Rodent Potency (HERP), that indicates what percentage of the TD_{50} in mg/kg/day a human gets from a daily lifetime exposure to a given chemical. We have also ranked possible carcinogenic hazards in the workplace based on the Permitted Exposure/Rodent Potency (PERP) index, using the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) as a surrogate for estimates of exposure.[27] The HERP or PERP index uses the same animal results and similar statistical methods as the usual low-dose linear estimation of risk; however, our purpose is to *compare* possible carcinogenic hazards from a variety of naturally–occurring and synthetic chemicals, not to perform risk assessments. As more theory is developed and more evidence is produced about the mechanisms of carcinogenesis, the ranking of hazards by the simple HERP index can be improved (as can risk assessment) by taking into account information on a given chemical, i.e., mechanism, shape of the dose–

response curve, and mutagenicity.

Our analysis of possible carcinogenic hazards suggests that the possible hazards of synthetic chemicals ingested from pesticide residues or water pollution appear to be trivial relative to the background of rodent carcinogens from natural and traditional chemicals (e.g., from the cooking of food or nature's pesticides in plant foods).

For occupational exposures, there is a 100,000-fold range in possible carcinogenic hazard for rodent carcinogens that have PELs.[27] For several compounds, the permitted exposures to workers are close to the TD_{50} value in rodents, indicating that these should be a high priority for regulatory attention. For high occupational exposures, little extrapolation is required from the doses used in rodent bioassays; therefore, assumptions about extrapolation are less important. This contrasts with the large extrapolations required for the low doses of human exposures to pesticide residues or water pollution.

Only a tiny fraction of the chemicals to which humans are exposed will ever be tested in rodent bioassays. One strategy for choosing chemicals to test is to prioritize chemicals according to how they might rank in possible hazard *if* they were to be identified as rodent carcinogens. A useful first approximation is the analogous ratio Human Exposure/Rodent Toxicity (HERT). HERT would use readily available LD_{50} values rather than the TD_{50} values used in HERP. LD_{50} is related to the MTD and the TD_{50},(30,31) and we have found that the ranking of possible carcinogenic hazards by HERP and HERT is similar.[32] The number of people exposed is also relevant when attempting to prioritize systematically among chemicals. Chemicals with high HERT and population exposure could then be investigated in more detail as to mutagenicity, mitogenicity, pharmacokinetics, and the like. Natural and synthetic chemicals should both be ranked. If natural chemicals in foods (e.g., chlorogenic acid in coffee, psoralens in celery, or indole carbinol in broccoli) turned out to be important, they might be bred out; for processed foods such as coffee, they might be extracted.

It is unlikely that the high proportion of carcinogens in rodent studies is due simply to selection of suspicious chemical structures: most chemicals were selected because of their use as industrial compounds, pesticides, drugs, or food additives. Moreover, historically our knowledge to predict carcinogenicity has been inadequate.[4] We have examined the proportion of chemicals in the CPDB that are positive for ten different data sets, and in each case, roughly half of the chemicals are positive according to the published author's opinion in at least one test (Table I): all chemicals in the CPDB, NCI/NTP chemicals, NCI chemicals reported before 1979, literature other than NCI/NTP, chemicals tested in both rats and mice (and among these, natural chemicals only and synthetic chemicals only), natural pesticides, mold toxins, and 22 chemicals in coffee.[1,2,4,17,26,29] Even if there is some selection bias, these results indicate that we are likely to be living in a sea of rodent carcinogens as defined by testing at the MTD.

Mechanisms of Carcinogenesis: Mutagenesis, Mitogenesis, and Carcinogenesis

The study of the mechanisms of carcinogenesis is a rapidly developing field that can improve regulatory policy. Both DNA damage and mitogenesis are important aspects of carcinogenesis, and increasing either substantially can cause cancer.[26,33–37]

Mutagens are often thought to be only exogenous agents; however, endogenous mutagens cause DNA damage (oxidative and other adducts) that can be converted to mutations during cell division. Endogenous rates of DNA damage are enormous. We estimate that the DNA hits per cell per day from endogenous oxidants are normally 10^5 in the rat and 10^4 in the human.[38–40] This promutagenic damage is effectively

TABLE I. Proportion of Chemicals Evaluated as Carcinogenic[A] for Several Data Sets in the CPDB[B]

1. Chemicals tested in both rats and mice	288/479 (60%)
1a. Naturally-occurring chemicals tested in both rats and mice	56/101 (55%)
1b. Synthetic chemicals tested in both rats and mice	232/378 (61%)
2. NCI/NTP chemicals[C]	
2a. NCI/NTP chemicals tested before 1979	60/117 (51%)
2b. NCI/NTP chemicals tested after 1979	105/198 (53%)
3. Chemicals tested in at least one species	
3a. Natural pesticides	29/57 (51%)
3b. Mold toxins	12/20 (60%)
3c. Chemicals in roasted coffee	19/26 (73%)

[A] A chemical is classified as positive if the author of at least one published experiment evaluated results as evidence that the compound is carcinogenic.
[B] CPDB = Carcinogenic Potency Database
[C] 94% (296/315) are tested by the National Cancer Institute/National Toxicology Program (NCI/NTP) in both rats and mice.

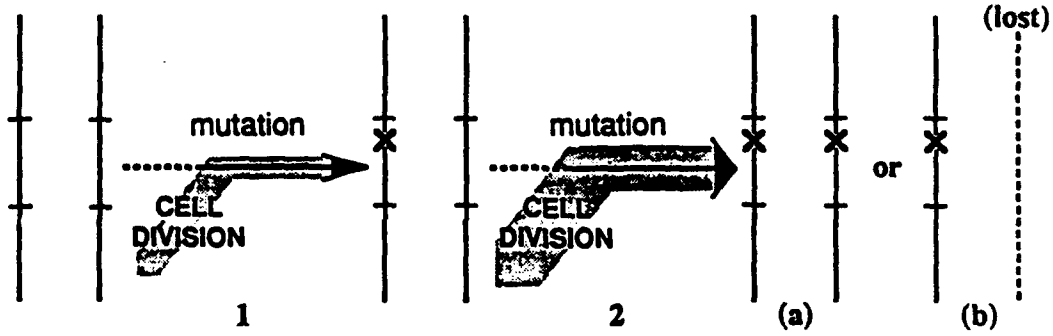

FIGURE 1. Mitogenesis increases mutagenesis. Mitogenesis (induced cell division) is a major multiplier of endogenous (or exogenous) DNA damage leading to mutation. The pathway to inactivating (x) both copies of a recessive tumor suppressor gene is shown (two vertical lines represent the pair of chromosomes carrying the genes). Cell division increases mutagenesis because of the following: DNA adducts are converted to mutations before they are repaired (1 & 2a); mutations owing to DNA replication (1 & 2a); and replicating DNA is more vulnerable to damage (1 & 2a). Mitotic recombination (2a), gene conversion (2a), and nondisjunction (2b) are more frequent, and the first two give rise to the same mutation on both chromosomes. This diagram does not attempt to deal with the complex mutational pathway to tumors.

but not perfectly repaired; the normal steady-state level of just 8-hydroxydeoxyguanosine (1 of about 20 known oxidative DNA adducts) in a 2-year-old rat DNA has been measured as 1/130,000 bases or about 90,000 per cell.[39] We have argued that this oxidative DNA damage is a major contributor to aging and to the degenerative diseases associated with aging such as cancer.[1,3] Thus, any agent causing chronic mitogenesis can be indirectly mutagenic (and consequently carcinogenic) because it increases the probability of converting endogenous DNA damage into mutations (Figure 1). Furthermore, endogenous rates of DNA damage are so high that it may be difficult for exogenous mutagens to increase the total DNA damage rate significantly by low doses that do not increase mitogenesis.

Geneticists have long known that cell division is critical for mutagenesis. If one accepts that mutagenesis is important for carcinogenesis, it follows that mitogenesis rates must be important. The inactivation of tumor suppressor genes is also known to be important in carcinogenesis, and recent evidence suggests that one of the functions of tumor suppressor genes is to inhibit mitogenesis.[41] When the first copy of a tumor suppressor gene is mutated, the inactivation of the second copy (loss of heterozygosity) is more likely to be caused by processes whose frequency is dependent on cell division (mitotic recombination, gene conversion, and nondisjunction) than by an independent second mutation.[1,2] Therefore, loss of heterozygosity will be stimulated by increased mitogenesis. Thus, while the stimulation of mitogenesis increases the chance of every mutational step, it is a much more important factor for tumor induction after the first mutation has occurred. This explains why mutagenesis and mitogenesis are synergistic[1,2] and why mitogenesis after the first mutation is more effective than before.

Thinking of chemicals as "initiators" or "promoters" confuses mechanistic issues.[42] The idea that "promoters" are not, in themselves, carcinogens is not credible on mechanistic grounds and is not correct on experimental grounds.[1,2,42] Every classical "promoter" that has been tested adequately (e.g., phenobarbital, catechol, TPA) is a carcinogen. The very word "promoter" confuses the issue because mitogenesis may be caused by one dose of a chemical and not by a lower dose. Dominant oncogenes and their clonal expansion by mitogenesis can clearly be involved in carcinogenesis, adding complexity; however, these mechanisms are still consistent with the view that mitogenesis is an important factor in carcinogenesis. Nongenotoxic agents (e.g., saccharin) can be carcinogens at high doses just by causing cell killing with chronic mitogenesis and inflammation, and the dose–response would be expected to show a threshold.[2,35,36] Epigenetic factors are also involved in carcinogenesis. However, both mitogenesis (e.g., through mitotic recombination) and DNA damage can cause loss of 5-methylC or other epigenetic modification.[2] Chronic mitogenesis by itself can be a risk factor for cancer: theory predicts it and the literature supports it.[2,43] The 40% of rodent carcinogens that are not detectable mutagens should be investigated to see if their carcinogenic effects at high doses result from induction of mitogenesis; if so, then such rodent carcinogens would be unlikely to be a risk at low doses.

Genotoxic chemicals, because they hit DNA, are even more effective than nongenotoxic chemicals at causing cell killing and cell replacement at high doses. Because genotoxic chemicals also act as mutagens, they can produce a multiplicative interaction not found at low doses, leading to an upward curving dose–response for carcinogenicity.[2,35,36] Mitogenesis can often be the dominant factor in chemical carcinogenesis at the high, nearly toxic doses used in rodent bioassays, even for mutagens. Mitogenesis can be caused by toxicity of chemicals at high dose (cell killing and subsequent replacement), by interference with cell–cell communication

at high dose,[44–47] by substances such as hormones binding to receptors that control cell division,[43] by oxidants (the wound healing response), by viruses, and such.[2] The important factor is not toxicity, but increased mitogenesis in those cells that are not discarded.

The importance of chronic mitogenesis for many of the known causes of human cancer has been discussed (e.g., hormones in breast cancer, hepatitis B[34] or C viruses or alcohol in liver cancer; high salt or *Helicobacter (Campylobacter)* infection in stomach cancer; papilloma virus in cervical cancer; asbestos or tobacco smoke in lung cancer; and excess animal fat and low calcium in colon cancer).[2,43,48] For chemical carcinogens associated with occupational cancer, worker exposure historically was often at high doses that might be expected to induce mitogenesis.

In animal cancer tests, chronic dosing at the MTD may often be the equivalent of chronic wounding, which is known both to increase carcinogenesis in animals and to be a risk factor for cancer in humans.[49] In the usual experimental design of dosing at the MTD and 1/2 MTD, both dose levels are high and may result in mitogenesis. Even at these two high doses, we have found that 44% of the positive sites in NTP bioassays are statistically significant at the MTD but not at 1/2 the MTD (among 365 positive sites). It is clear that the mechanisms of action for all rodent carcinogens are not the same and that one cannot use a simple, linearized, risk assessment model for all of them. For some chemicals, there is evidence to support mitogenesis effects unique to high doses (e.g., formaldehyde, melamine, and saccharin). For others (e.g., butadiene), carcinogenic effects have been found 100 times below the MTD. Further studies of mechanism in rodent bioassays should help to clarify such differences. Adding routine measurements of mitogenesis to the 13-week toxicology study and the 2-year bioassay would provide information that would improve dose setting, interpretation of experimental results, and risk assessment. The work of Cunningham et al.[50,51] is a good example of how mechanism studies help to differentiate among chemicals. Their experiments showed that with pairs of mutagenic isomers (1- versus 2-nitropropane and 2,4- versus 2,6- diaminotoluene), one isomer is a carcinogen and the other is not; however, only the carcinogen was mitogenic.

Qualitative Extrapolation Between Species

Prediction of Positivity

How well can one predict carcinogenicity from rats to mice or from mice to rats? These closely related species both receive doses at or near the MTD in chronic bioassays. Because humans are less closely related to rodents, qualitative prediction from results in rats or mice to humans exposed at high doses is not likely to be more accurate than prediction between rats and mice.

TABLE II. Comparison of Carcinogenic Response for 479 Chemicals Tested in Both Rats and Mice

Not positive in either rats or mice	191
Positive in rats only	59
Positive in mice only	64
Positive in both rats and mice, no common target site	57
Positive in both rats and mice at same target site	108[A]

[A]For 47 of these 108 chemicals, the liver is the only site in common between rats and mice.

Using results in the CPDB for the 479 chemicals that have been tested in both rats and mice, Table II indicates that if a chemical is positive in one of the species, it will be positive in the other species about 75% of the time. This is similar to results reported earlier for smaller numbers of chemicals.[4,5,52–54] Because about half of the test chemicals are positive in each species, by chance alone we would expect a positive predictive value between species of about 50%.[4,5] Thus, the overall predictive values of 75% between rats and mice provide only moderate confidence in interspecies extrapolation. We have also compared results for the limited number of compounds tested in hamsters and rats or hamsters and mice. Prediction from rats to hamsters or from mice to hamsters (about 65%) is similar to, but slightly less accurate than, prediction between rats and mice.

We have discussed three factors that influence the accuracy of prediction of carcinogenicity between rats and mice. Predictive values are more accurate for mutagens than nonmutagens and for chemicals that are toxic at lower doses compared to higher doses (as measured by the MTD). The accuracy of prediction also varies by chemical class.[4]

Prediction of Target Site

If a chemical is positive in one species, how often will it be positive in the other species and at the same target site? Because many chemicals induce tumors at multiple sites, there is often more than one target site that is potentially a common site for the two species, thus increasing the chance that there will be some target site in common.

Site-specific prediction between rats and mice is less accurate than overall prediction of positivity. Knowing that a chemical is positive at any site in one species gives about a 50% chance that it will be positive at the same site in the other species (Table II). For 47 of the 108 chemicals with a site in common between rats and mice, the liver is the only site in common. Site-specific prediction from rats or mice to hamsters is similar to that between rats and mice.

Ultimately, one wants to know whether chemicals that have been shown to be carcinogenic in experimental animals are also carcinogenic in humans. This question cannot be answered by reversing the question (i.e., by asking whether chemicals that are human carcinogens are also carcinogenic in a rodent species) because even if most human carcinogens

are rodent carcinogens, the converse does not necessarily follow, as can be demonstrated by a simple probabilistic argument.[55] However, some additional evidence about interspecies extrapolation can be obtained by asking how good a model the human is for the rat or the mouse, even though this will not provide direct evidence about how good a model the rat or mouse is for the human. The evaluations of the International Agency for Research on Cancer (IARC)[56] list 55 known human carcinogens including industrial processes, therapeutic combinations, single chemicals, and mixtures such as tobacco smoke.[56–58] For 35 of these, data in experimental animals have been evaluated by IARC.[57] The CPDB includes only results of experiments on single chemicals, administered by routes expected to result in whole-body exposure, that meet specified experimental-design criteria. A search of the CPDB indicates that results are included for 17 human carcinogens tested in rats and for 16 tested in mice. Using only these CPDB results, the overall predictive value from humans to rats is 76% (13/17) and from humans to mice is 75% (12/16). For some human carcinogens with only negative results[A] in the CPDB, positive results have been obtained in experiments not meeting CPDB inclusion criteria.[58] Prediction based on target organ is 47% (8/17) from humans to rats and 37% (6/16) from humans to mice. Thus, the overall predictive values are similar to those reported above between rats and mice for the CPDB; the value for target organ is slightly lower for mice.

Based on this experimental evidence from the CPDB involving prediction from rats to mice, from rats or mice to hamsters, and from humans to rats or mice, we conclude that one cannot assume that if a chemical induces tumors at a given site in one species it will also induce tumors at the same site in a second species; the likelihood is at most 49%.

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[A] In rats, 4 human carcinogens have only negative results in the CPDB: arsenic compounds, azathioprine, cyclosporin, and Myleran. All 4 are evaluated by IARC as having limited, not sufficient, evidence of carcinogenicity in experimental animals. In mice, 4 human carcinogens have only negative results in the CPDB. IARC evaluates 2 as having limited evidence in animals (arsenic compounds and cyclosporin) and 2 as having sufficient evidence (aflatoxin and nickel compounds). Some rodent experiments on human carcinogens are used by IARC in their evaluations but are not included in the CPDB because of route of exposure (e.g., skin painting, subcutaneous injection, intratracheal instillation, implant), nonchronic dosing, use of infant animals, lack of controls, cocarcinogenesis tests, and screening assays on the accelerated induction of tumors.

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Conservatism in Carcinogen Risk Assessments?

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The following is the abstract of the presentation by Mr. Bailar. His paper is not available for publication at this time.

Present methods of assessing the human health risks of carcinogens at low exposure levels are likely, on the whole, to underestimate those risks. In this context, "low exposure levels" means exposures where the assessed risks are 10^{-5} or lower. The process of risk assessment in this range is widely recognized, especially by its practitioners, to be subject to much uncertainty, often orders of magnitude. Neither supporters nor critics have a "gold standard" to assess the performance of various steps in the process. There are several strong reasons, however, for believing that risks overall may well be greater than estimated.

First, there are at least six plausible biologic mechanisms that produce supralinear dose–response curves. Each of these has been shown in practice to be important at higher risk levels in some risk assessments, and none has been ruled out as being of broad importance. In fact, data from the National Toxicology Program show that underestimates with the one-hit model are almost as common as overestimates.

Second, uncertainty in risk assessment is commonly expressed on geometric (logarithmic) scale, such as "within an order of magnitude," but what matters for the protection of human health is risk on a linear scale. For example, the consequences of underestimating risk by a factor of 10 or 100 are 9 or 99 times greater than the consequences of similar overestimation. Thus, an argument that overestimation is more common, even (contrary to evidence) by a wide margin, is compatible with an overall result that is far from conservative.

Third, when the data as a whole are deemed to be compatible with a supralinear model (not just a matter of showing that a linear or one-hit model fails to fit), one generally has no way to estimate where the curve starts to "flatten out" and hence no way to derive an upper bound on risk at much lower levels. This situation seems to be quite common: A linear model fitted to one high-dose point, or even two if there is some evidence of flattening at the upper end, is compatible with very large risks at lower doses even if those risks are sublinear because an upper bound in that range cannot be calculated.

Fourth, we do have a human health problem. Cancer incidence rates are known to be rising everywhere that adequate epidemiologic data exist; cancer death rates at older ages are rising even when lung cancer is excluded from the data, and geographic differences in risk cannot be explained by inherent differences in susceptibility. A high proportion of persons now get at least one cancer at some time during their lives, and something external is causing most of them (perhaps 85%) or we would not find such large variations in risk over space and time.

Recent arguments that risk assessment methods on the whole overestimate hazards to human health are not and will not become credible unless they can be revised to respond to the concerns expressed above. On the basis of current evidence, it is more likely that standard methods underestimate risk, despite some recent and well-publicized exceptions.

Uncertainties in Risk Assessment

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Current risk assessment practices largely reflect the need for a consistent set of relatively rapid, first-cut procedures to assess "plausible upper limits" of various risks. These practices have important roles to play in 1) screening candidate hazards for initial attention and 2) directing attention to cases where moderate-cost measures to control exposures are likely to be warranted, in the absence of further extensive (and expensive) data gathering and analysis.

A problem with the current practices, however, is that they have led assessors to do a generally poor job of analyzing and expressing uncertainties, fostering "One-Number Disease" (in which everything from one's social policy position on risk acceptance to one's technical judgment on the likelihood of different cancer dose–response relationships is rolled into a single quantity). At least for analyses that involve relatively important decisions for society (both relatively large potential health risks and relatively large potential economic costs or other disruptions), we can and should at least go one further step — and that is to assess and convey both a central tendency estimate of exposure and risk as well as our more conventional "conservative" upper-confidence-limit values.

To accomplish this, more sophisticated efforts are needed to appropriately represent the likely effects of various sources of uncertainty along the casual chain from the release of toxicants to the production of adverse effects. When the effects of individual sources of uncertainty are assessed (and any important interactions included), Monte Carlo simulation procedures can be used to produce an overall analysis of uncertainties and to highlight areas where uncertainties might be appreciably reduced by further study. Beyond the information yielded by such analyses for decision-making in a few important cases, the value of doing several exemplary risk assessments in this way is that a set of benchmarks can be defined that will help calibrate the assumptions used in the larger number of risk assessments that must be done by "default" procedures.

Introduction

To communicate with some degree of clarity on the subject of uncertainty, it is necessary to offer some basic definitions and distinctions from related concepts. In this paper, "uncertainty analysis" means an attempt to fairly assess and convey how likely it is that the estimated value of a particular parameter differs by various amounts from the "truth." A description of uncertainty, therefore, is a description of the imperfection in knowledge about something that is conceived of as having some "true" single value in some inaccessible reality. "Uncertainty analysis" must be distinguished from another concept that is also described with the aid of probability distributions. "Heterogeneity" or "interindividual variability" is the distribution of true values of a parameter that would be found in a population by perfectly accurate measurement techniques. For example, weighing a set of individuals with an excellent scale will not obtain the same results for different people. People really do differ in their weights (and other characteristics that affect individual risks) and no degree of improvement in the measuring instrument will make them all the same. The difficulties of knowing the degree of interindividual variability in susceptibility to toxicants in a population is one factor that contributes to uncertainties in assessing risks particularly for noncancer effects.[1]

First, some policy questions related to uncertainty analysis will be discussed, i.e., what is it potentially good for, and why is this such a touchy subject? This will be followed by some historical speculations on why many of those who were brought up in the 1940s to the 1960s and received technical training in the 1960s through the 1980s find the prospect of quantitatively assessing uncertainties foreign and troubling. An extended example will be offered which addresses the uncertainties in a practical risk assessment context; the example compares potential carcinogenic risks of drinking water from two sources: an "Advanced Water Treatment" system developed for the City of San Diego and a particular reservoir supplied from the Colorado River. Finally, some general caveats and warnings are offered about the "brave new world" of enhanced analysis of uncertainties in risk analysis.

Uncertainty Analysis: Policy Considerations

A good analysis of uncertainties serves policy goals of 1) "bounding the set of not clearly incorrect answers"[2] and 2) allowing the reader of a set of risk assessment results to "make as informed a decision on risk acceptance or control as if the reader him/herself had gone through the process of doing the risk assessment."[3] An appropriate analysis of uncertainties brings into the open the expected consequences

of standard summary treatments of uncertainties in different factors affecting risk, thus allowing greater scope in making risk control choices from among options that are expected to limit risk to various extents with different degrees of confidence.

The particular form of expression of uncertain results that is most relevant for policy-making depends on the legislative mandate of a particular program or type of decision. Changing the form for expressing uncertainty for specific regulatory purposes requires careful examination of whether one is changing the protective posture of the agency in implementing the intent of the law in question. Legislation that calls on an agency to "protect public health with an adequate margin of safety" may well be interpreted as directing the agency to pay attention to the level of risk that, in the judgment of agency analysts, will not be exceeded with relatively high confidence (99% or possibly more); in contrast, a statute calling for a cost/benefit balancing may well be interpreted as requiring the agency to pay attention to the mean "expected values" of the distributions of the estimates of risk and economic costs.

Ideally, an analysis of uncertainty is not an afterthought that one gets from the statistician after the rest of the work on a risk assessment has been completed. It should really be part of the "warp" and "woof" of each step in the analytical process that carries some uncertainty (i.e., everything but the arithmetic and sometimes the arithmetic, too). Thus, among the reasons this subject is sensitive are 1) it matters to the substantive protective posture for managing risks and 2) it has the potential to change the way a substantial number of technical analysts do their jobs.

Historical Attitudes Toward Uncertainties in Scientific Information

Many scientists involved in risk issues have some reluctance to attempt to quantify their uncertainties; this may derive from the cultural assumptions about science that prevailed when they were growing up and making the lifetime commitment to become scientists. Recent changes in these cultural assumptions are a likely source of a feeling among scientists that the understandings under which they chose science as a career have been altered, and not for the better.

One popular scientific attitude toward uncertainties present in the 1950s, when many of today's scientists were children, is typified by detective Joe Friday's saying, "Just the facts, ma'm, nothing but the facts." Joe Friday was not a scientist, of course, but we do not recall Mr. Wizard being uncertain about anything either. A favorite example, however, is from a classic early 1950s science fiction movie called *THEM* in which giant ants have been produced as the result of mutations of ordinary ants following exposure to radiation from the atomic bomb testing. This fact is not known at the beginning, of course. The local police and the FBI man only know that people are showing up horribly mutilated and smelling of formic acid; there is also a strange print cast from the desert sand near one of the victims that no one is able to identify. Sending the print to Washington brings, on the return flight, the stereotypical absent-minded professor who, with his lovely daughter (also a Ph.D.), proceeds to investigate. The father and daughter team assemble information but share absolutely nothing with the local police and the FBI agent who had called for help in the first place. The reason for their behavior is quickly explained. They do, indeed, have a theory. They are, in fact, specialists on ants, and formic acid stings are evidently the way ants kill. However, they are duty-bound as scientists not to share their theory until they are certain, even though giant, man-killing ants may be multiplying in the desert. Why? Because it might cause panic. One might think that at least some limited contingency planning might be done on the basis of tentative information, but apparently this was not the prescription for scientific behavior in the early 1950s.

In the 1990s, of course, we are expected to deal with hazards that are a great deal more subtle, with information that is less complete than was available in the movie about the giant ants. By today's standard of conduct, the two scientists in the movie should have said, "Incredible as it seems, there is a good chance that somehow a colony of giant ants has developed out there in the desert." Perhaps they would even state, "Based on the way that print looks and the circumstance of the formic acid, we think there may be an 80% chance that there are giant ants out there. What the other 20% possibility might be, we can't guess, but we give the ant possibility about 0.8."

On pain of usurping the autonomy of the civil authorities to exercise their authority in representing community value/policy preferences, the scientist is called upon to disclose information of potential social significance while it is still somewhat uncertain. Hopefully, this is done with as much attendant communication about the alternative possible states of the world, and the implications of these alternatives, as would be helpful in the decision-making process. The scientist must not arrogate the sole authority to make the relevant decisions. By withholding information on possible states of the world with potential implications for decision-making, the scientist would be doing just that.

A Practical Example of Uncertainty Analysis

Over the past few years, John Froines and others at UCLA have been measuring the concentrations of a number of contaminants in two potential sources of drinking water for the City of San Diego:

- The Miramar reservoir (MIRA), which contained chlorinated water derived from the Colorado River.
- The output of an advanced water treatment (AWT) system that recycles sewage.

We considered three different sources of uncertainty in our

analysis:

- Uncertainty as to which pollutants are actually present in the two water sources, after taking into account the measurement difficulties encountered in the study and the sensitivity with which different chemicals can be reliably detected.
- Uncertainty in the long-term average amounts of each carcinogenic pollutant present.
- Uncertainty in the potency of each carcinogenic pollutant for producing cancer in humans, i.e., how many cases of cancer should be expected per unit of lifetime average consumption?

The combined effects of uncertainties of the latter two types for all studied contaminants were calculated with the aid of a Monte Carlo simulation.

In a Monte Carlo simulation, the combined effects of different sources of uncertainty are assessed by randomly drawing values from distributions intended to represent different uncertain parameters that affect risk. For example, imagine that we are uncertain about both the concentration of a pollutant in water and the number of cases that might result per unit concentration (the carcinogenic potency). For each "trial" of a Monte Carlo simulation, a value is randomly selected from 1) a statistical distribution that represents our uncertainty in concentration and 2) another statistical distribution that represents our uncertainty in the cancer potency. Together with an assumption about the amount of water consumed per day or per lifetime, this leads to a prediction of the cancer risk from that chemical for that trial. By repeating this procedure for hundreds or thousands of trials, one obtains a picture of how likely it is that the cancer risk from each chemical might take on various values. Calculations of overall risk from multiple chemicals are added within each trial.

We chose not to include in our first-cut analysis one other uncertain parameter that directly bears upon the risk: the amount of water that people consume. All calculations were for the risk expected if exposed people consumed a standard 2 L of water per day for their entire lifetimes.

Which Pollutants Are Actually Present?

For the most part, the contaminants that were considered to be present in each water system were those that were reliably detected utilizing a criterion based on the standard error of the difference between the long-term average concentration in the sampled water and a set of concurrent "travel blanks." In our final analysis, we chose to depart from this procedure in one case. Arsenic, as it happens, dominates the overall risk for the MIRA water. In order to avoid overstating the difference in risk that the data could really show between MIRA and AWT water, we chose to retain arsenic in the AWT calculations. This allowed us to illustrate the level of risk that might be possible from AWT water if arsenic were, in fact, present at the levels indicated, even though those levels were not sufficient for reliable detection of arsenic in AWT water. Thus, the way we analyzed and presented uncertainties was affected by the type of intended risk comparison.

Representing Uncertainties in the Concentrations of Pollutants in the Waters

In many cases, the long-term average values of the travel blanks were similar in order of magnitude to the long-term average values of the AWT and/or MIRA water samples. Because of this, the best expected value for the long-term average concentrations had to be arrived at by subtracting the blank averages from the sample averages. When subtracting two numbers of roughly equal size, the resulting uncertainty is likely to be best described by a normal distribution. Therefore, our basic representation of uncertainties in the concentration values was a normal distribution with a standard deviation calculated from the standard deviations of the blanks and the sample means.

This needed to be modified somewhat because it made no sense to allow the distribution of concentrations to take on negative values. Therefore, in the course of the Monte Carlo simulations, wherever a negative value would otherwise be selected from the normal distribution, we instructed the computer to substitute zero.

Representing Uncertainties in the Carcinogenic Potency of Different Carcinogens

In work previously conducted for the National Institute for Occupational Safety and Health, we performed a series of three case studies (perchloroethylene, ethylene oxide, and butadiene) incorporating pharmacokinetic modeling of the delivered doses of putative, genetically acting agents or genetically active metabolites to improve the assessment of likely low-dose carcinogenic risks.[4–7] One of the innovative aspects of these studies was attempts to make "best" (or "least unlikely") estimates of risk in addition to more usual "plausible upper limit" estimates. Table I summarizes the basic approaches used to arrive at these different estimates of risk. Table II shows the basic comparison of the results of these more elaborate analyses to the results of more standard, upper-confidence-limit-only risk assessments by the U.S. Environmental Protection Agency's (EPA) Carcinogen Assessment Group.

As might have been expected, the estimates of the most likely values of the carcinogenic risk were considerably below the plausible upper limit values, although the upper confidence limit estimates of cancer potency were similar between our studies and those of EPA (Table II). The summary analysis in Table III indicates that, on average, the "least unlikely" estimates of cancer risk in these studies were about 7% of the "plausible upper limit" risk estimates. The lower portion of Table III shows how we reasoned further from this difference to obtain a likely distribution of cancer potency

TABLE I. Assumptions for Derivation of "Least Unlikely" and "Plausible Upper Limit" Cancer Potency Estimates for Putative Genetically Acting Agents

"Least Unlikely" Estimates
- "Best-estimate," physiologically based, pharmacokinetic models for estimation of metabolic activation and/or the persistence of active metabolites in the system.
- Expression of "delivered dose" as either the amount of active metabolite per (body weight)$^{3/4}$, or the internal concentration X time product of the direct-acting agent for interspecies projections.
- Calculation of "maximum likelihood estimates" (MLE) of the coefficients of the multistage model for individual tumor sites, summed for all sites. But an assumption of a modest amount of background interaction is introduced where the MLE linear terms (q_1s) for all sites are zero to produce a finite low-dose linear term.
- Calculation of the geometric mean of expected low-dose risk as predicted by data from experiments on different species and genders of animals.

"Plausible Upper Limit" Estimates
- Plausible high-risk-predicting pharmacokinetic models.
- Expression of delivered dose per (body weight)$^{2/3}$ for interspecies projections.
- 95% upper confidence limit estimates of the linear term from a multistage model fit in the most sensitive species and gender of animals tested.

estimates that we could use for Monte Carlo simulation analysis.

We began with a basic decision to treat our uncertainties in this parameter as lognormally distributed; i.e., the logarithms of the distribution of likely cancer potency values are normally distributed, as is illustrated in Figure 1. This was because in our judgement the different sources of likely error that contributed to our uncertainties in carcinogenic risk for individual chemicals (e.g., the relative amounts of absorption of toxicants in people and rodents; relative rates of elimination from the body; rates of metabolic activation to toxic metabolites; and inactivation to safe metabolites, cell replication, and DNA repair rates in animals and humans) all will tend to exert relatively independent, multiplicative effects on the level of likely human risk relative to the risk inferred directly from animal experiments (which are the source of most of the cancer potency estimates). The consequence of multiplying together a series of uncertain parameters is that the resulting overall uncertainty will tend to be lognormal. This is because 1) multiplying a series of uncertain parameters is the same as adding their logarithms and 2) by the "central limit theorem" of probability and statistics, the uncertainty in the sum of a large series of uncertain parameters takes on the standard "normal" or "Gaussian" form.

Given the choice of the lognormal form, we needed to determine how likely it was that the true cancer potency for a given chemical was equal to or above the EPA "plausible upper bound" cancer potency factor. It is important to understand that the EPA values, although calculated with "conservative" assumptions that are expected to overstate risk most of the time, cannot be expected to always overstate risk.

- For example, EPA routinely uses the most sensitive species tested for estimating human risk; however, in general, where only two other species are tested (rats and mice), there is nothing to prevent humans from being more sensitive than the more sensitive of the two rodents, at least for some modest proportion of all carcinogens.
- Standard risk assessment procedures that do not use

TABLE II. Comparisons of Results of Pharmacokinetic-Based Risk Analyses with EPA Projections of Low-Dose Risks (all data in lifetime risks for occupational exposure to 1 ppm, 8 hours/day, 5 days/week for 45 years)

Chemical	"Best (Least Unlikely) Estimate"	"Plausible Upper Limit Estimate"
Results from Pharmacokinetic-Based Risk Analyses:		
Ethylene oxide	0.0065	0.019
Butadiene	7.9E-4	0.032
Perchloroethylene	6.7E-4	0.013
Results from More Usual EPA/CAG Risk Analyses from Animal Data:		
Ethylene oxide	Not done*	0.028
Butadiene	Not done	0.098
Perchloroethylene	Not done	0.0033

*Implicitly, a best estimate equivalent to a lifetime risk of 0.104 was calculated from two observed human leukemias in the Hogstedt et al. (1986) study. This is a central tendency estimate because no statistical upper-confidence-limit procedure was used in computation.

TABLE III. Uncertainties in Carcinogenic Risk Estimates for Genetically Acting Agents, as Inferred from Three Case Studies of PBPK[A]-Based Risk Analyses

Compound	Hattis "Best Estimate"	Hattis "Plausible Upper Limit"	EPA UCL[B] CPF[C]	Hattis Best/ Hattis UCL Ratio	Hattis Best/ EPA UCL Ratio
Ethylene oxide	0.0065	0.019	2.80E-02	0.342	0.232
Butadiene	0.00079	0.032	9.80E-02	0.025	0.008
Perchloroethylene	0.00067	0.013	3.30E-03	0.052	0.203
			Geom. Mean	0.076	0.072
			Geom. Std. Dev.	3.881	6.703
			Geom. Std. Err.	2.188	2.999

If we take the EPA UCL estimate of risk as approximately a 95th percentile value (1.6449 standard deviations above the median), and if we represent our uncertainties as lognormally distributed about a median estimate at approximately 0.072 times the EPA UCL, then the geometric standard deviation of the lognormal distribution representing our uncertainties is $10^{[\log(0.724)/1.6449]} = 4.93$.

[A]PBPK = physiologically based pharmacokinetic model.
[B]UCL = upper confidence limit.
[C]CPF = cancer potency factor.

pharmacokinetic analysis may understate risk if, as in the case of vinyl chloride, there is a saturation at high doses in the metabolic activation of the carcinogen, leading to a plateau at high doses in the percentage of animals that develop tumors. If only the two highest dose points had been available for vinyl chloride (as would have been the case if the vinyl chloride data available for risk analysis had come solely from the usual National Toxicology Program for chronic animal bioassay), the low-dose slope of the cancer dose–response relationship would probably have been underestimated by about fivefold.

- If there are appreciable differences among humans in overall individual susceptibility, as there seem to be in many specific parameters that can be expected to affect susceptibility, this would be expected to increase the population risks of humans exposed at relatively low-dose levels relative to what would be expected for a completely uniform population of "median-susceptible" individuals.[8,9] This factor is not included in EPA's calculations, but it can routinely be expected to increase low-dose population risks to a diverse community of humans relative to the risks of the relatively uniform groups of rodents that are tested at high doses.

In the light of these various possibilities, we chose to treat the EPA upper confidence limit (UCL) cancer potency estimates derived from animal data as the 95th percentile of our distribution of uncertainties in cancer potency. As listed at the

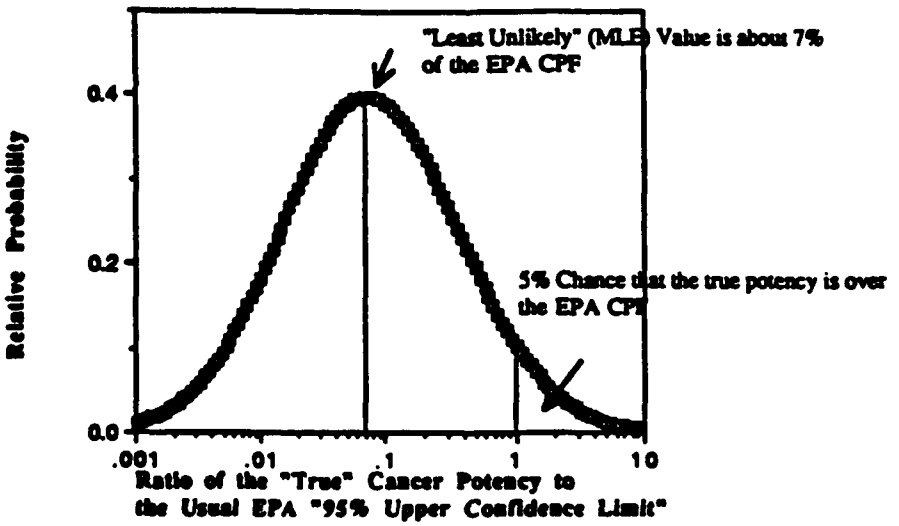

FIGURE 1. Log plot of the estimated likelihood distribution for cancer potency factors (CPF) for genetically acting carcinogens. (MLE = maximum likelihood estimate.)

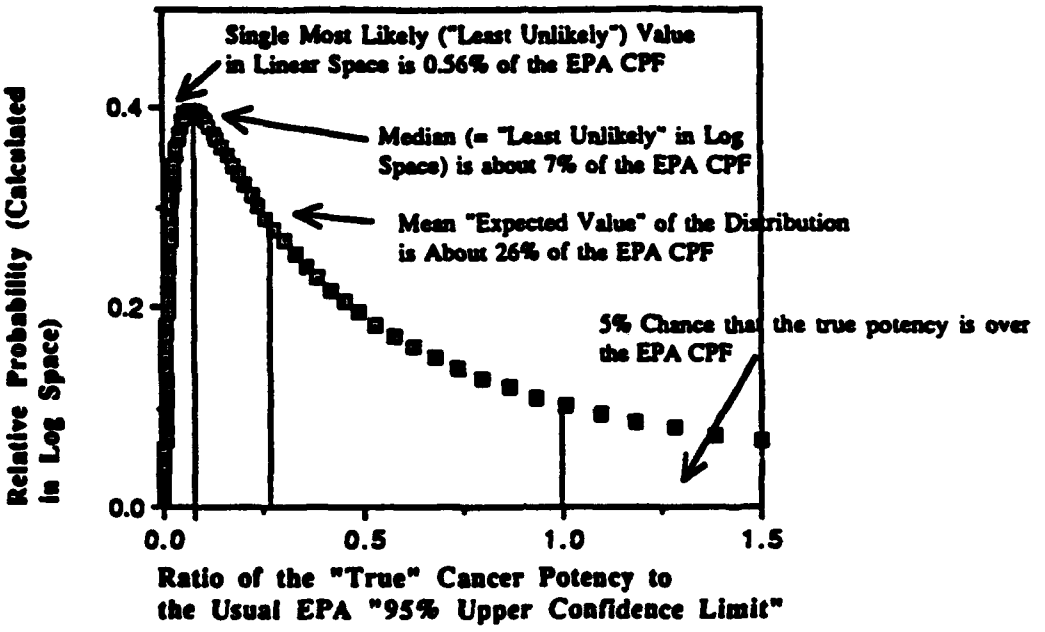

FIGURE 2. Linear plot of the estimated probability distribution for cancer potency factors (CPF) for genetically acting carcinogens. (MLE = maximum likelihood estimate.)

bottom of Table III, because the 95th percentile of a normal distribution is located about 1.64 standard deviations above the mean, it follows that a lognormal distribution with a 95th percentile value located 1/0.0724 = 13.8 times above the geometric mean must have a geometric standard deviation of about 4.93, or in other words, the standard deviation of the logarithms of our distribution of potency values is the log of 4.93, or about 0.6931.

Figure 2, which is a replot of Figure 1 on a linear axis rather than a log axis, illustrates some important properties of a lognormal distribution. It can be seen that the distribution is skewed (is asymmetrical with a long tail) to the right. Because of the asymmetry, the single most likely value (or as we prefer to term it, the "least unlikely" estimate) is not an unbiased estimate of the average or mean value of the distribution as a whole. If one were doing a classic cost–benefit assessment of various options for control of exposure, it is the mean, rather than the most likely value, that is the most relevant parameter for describing the "expected value" of the health improvements that might be obtained from the choice of one control option over another. The mean of the distribution is the average of all the potency values, weighted by their relative probability of being true (at least as represented by our lognormal assumption). This was completely missed in a recent, highly controversial critique of EPA risk assessment practices by the Federal Office of Management and Budget.[10]

The difference between the mean and the most likely value can be illustrated with a gambling analogy. Imagine that a person has the opportunity to participate in a lottery at a cost of $1.00 with a 1/10,000 chance of winning $100,000. The single most likely value of the return from this wager is zero, because there are 9999 chances of losing and only 1 chance of winning. However, the mean or expected value of the wager is $10.00 ($100,000 • 1/10,000+$0 • 9,999/10,000). *Caveat*: the "utility" of the wager to a specific person could be greater or less than $10.00, depending on the person's positive or negative enjoyment of the gamble itself, and whether $10,000 is worth exactly 10,000 times $1.00 in the person's own psychic calculus of value.

Overall, as seen in Figure 2, the mean of the lognormal distribution we have used as our best estimate of our uncertainty in cancer potencies is about 3.5 times greater than the most likely value, or, in other terms, a little more than 25% of the original EPA UCL. Thus, if our sparse set of three case studies is giving us an accurate picture of the general uncertainty in cancer potency estimates, and if the other assumptions we have made hold, the best expected value of cancer risk is only about fourfold less than the EPA UCL. What is our uncertainty in the original 7.2% ratio that was the result of our three case studies, and how would differences in this ratio affect our conclusion that a mean estimate of risk is only fourfold less than the EPA UCL? Conceivably, other carcinogens (perhaps some that do not act by direct genetic mechanisms, e.g., 2,3,7,8-tetrachlorodibenzodioxin) would have larger differences between a best estimate of cancer risk and the EPA UCL. Figure 3 shows the result of assuming a wide array of different ratios for the 7.2% best estimate from our three case studies, keeping all of the rest of the reasoning constant. It can be seen, surprisingly, that as one increases the distance between the UCL and the best estimate of potency much below about 6.7%, the ratio of the mean to the UCL

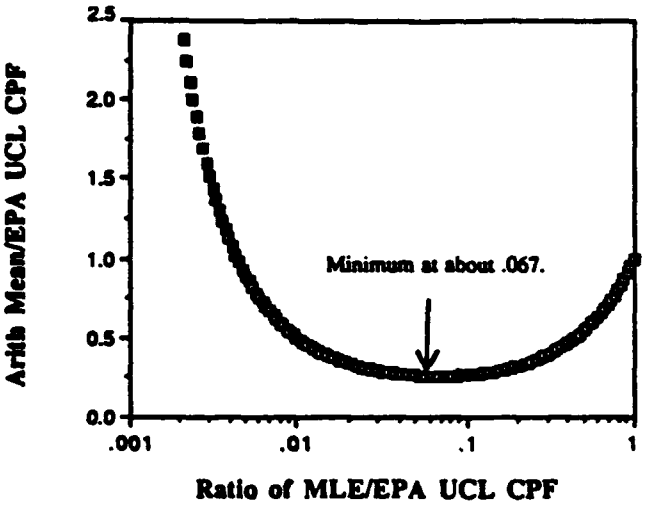

FIGURE 3. Influence of the MLE/CPF ratio on the "expected value" (mean) of a lognormal distribution of cancer potency factors (CPF).

starts to rise. This is because one necessarily increases the estimate of the geometric standard deviation, and below about the 6.7% point in the curve, the small but increasing likelihood of very large risks (far over the UCL) begins to outweigh the reduction of risk in the central/lower portion of the curve in the calculation of the overall mean.

A final and difficult point of methodology comes when we consider the small number of carcinogens (e.g., arsenic, benzene) whose cancer potency estimates are based on human epidemiological data by EPA, rather than on animal data. Because EPA estimates from human data are effectively maximum likelihood estimates, in these cases, we must take the EPA cancer potency value itself as our best estimate of risk. In the first simulations, however, we have elected to retain the same estimate of overall uncertainty as we use for the animal data. This is partly because, although the human-based estimates do not suffer from the difficulties and uncertainties inherent in animal-to-human projections, they have their own peculiar difficulties (especially related to the accuracy of the assessment of past individual exposures, the healthy worker effect, the effects of truncation of the period of observation following exposure, and the assessment of the interacting effects of potentially confounding exposures). These difficulties may often cause complications and even downward biases that are as serious as those produced in the extrapolation of animal data. Because of the importance of arsenic (whose cancer potency is based on human data) in our overall analysis, this particular judgment seriously influences the risk estimates below. We, therefore, also present below the results of a series of Monte Carlo simulation runs in which we assume that there is no uncertainty about the EPA estimate of the cancer risk from inorganic arsenic.

Tables IV and V give the Monte Carlo simulation results with and without the assumption of uncertainty in the arsenic cancer potency value. The Monte Carlo simulations were done using "Crystal Ball" simulation software (Version 1.04, Market Engineering Corporation, Denver, Colorado) for the Macintosh. Each run consisted of 5000 individual trials. Shown in these tables are the median, the mean, and the 95th percentiles of the calculated risk distributions for each chemical separately, for some aggregates of different chemicals, and for the total risk. The median is simply the middle value of each distribution of 5000 values which, if our assumptions are correct, has a 50% chance of being either larger or smaller than the true risk. The mean is the average of all 5000 values. Finally, the 95th percentile (the average of the 250th and the 251st highest of the 5000 values) is the level of risk which, if we have represented all of the uncertainties appropriately, has only a 5% chance of being smaller than the true risk. (The small differences in specific quantities that should be analogous in these two tables are due to statistical fluctuations in the results obtained in separate runs of 5000 trials each.) Comparing the results in the two tables, it can be seen that the assumption of uncertainty in the arsenic potency has a substantial influence both on the mean and high-percentile estimates of the risk and on the overall uncertainty of the risk results, i.e., the spread between the median and 95th percentile risks.

These tables give a glimpse of what might be expected if the "brave new world" of expanded use of Monte Carlo simulation for analysis of uncertainties ever arrives. One may well ask how one discusses the risk management implications of findings such as these. In presenting our work to the sponsors, we offered the following interpretive conclusions:

> "Overall, the risk analysis presented here gives some reason for concern for the long-term use of the MIRA (raw Colorado River) water supply, at least to the degree that the concentrations we measured in the reservoir samples accurately represent what is likely to be present in the finished water delivered to consumers. The overall mean estimate of lifetime risk from 2 L/day consumption is about 3 cancers per 10,000 people.[A] About 98% to 99% of this risk is derived from the presence of inorganic arsenic; trihalomethanes from chlorination represent the bulk of the remaining assessed carcinogenic risk. (The concentration of arsenic in MIRA water is well within applicable federal and state standards; however, at least at the state level, the arsenic water standards are in the process of being reevaluated.)
>
> "Our overall MIRA risk estimate is significantly

[A]We highlight the mean estimate of risk here because this is the measure of risk that would correspond to the "expected value" of risk, which might be used in a cost–benefit analysis. Higher percentiles of the risk distribution (e.g., the 95th percentile) would increase in importance for those people who wish to attach extra value to modest probabilities that the true risk might be considerably larger than the estimate of the mean risk.

TABLE IV. Results of a Monte Carlo Simulation Run (5000 Individual Trials) of Lifetime Cancer Risks from 2 L/Day Water Consumption — Assuming that the Uncertainty in the Cancer Potency of Arsenic is the Same as the Uncertainty in the Potency of Other Carcinogens

Data Set	50th Percentile (median) Risk	Arithmetic Mean Risk	95th Percentile Risk
MIRA Water			
Bromoform	1.5E-6	5.4E-6	2.2E-7
Chloroform	2.6E-8	9.5E-8	3.9E-7
Dibromochloromethane	5.4E-7	2.0E-6	7.7E-6
Bromodichloromethane	1.0E-6	3.6E-6	1.4E-5
Subtotal, all trihalomethanes	2.5E-6	5.7E-6	2.0E-5
DEHP	1.1E-7	4.4E-7	1.9E-6
Subtotal, all organics	3.0E-6	6.1E-6	2.1E-5
Arsenic	7.7E-5	3.0E-4	1.1E-3
Total	8.4.E-5	3.1E-4	1.1E-3
AWT Water			
DEHP	2.0E-7	7.8E-7	2.9E-6
*(Arsenic)**	*3.4E-6*	*2.3E-5*	*9.1E-5*
Total	4.3E-6	2.4E-5	9.2E-5

*Caveat: Arsenic is not present in AWT water in amounts that are detectable with any confidence or reliability. These results are shown to illustrate the limitations, in terms of overall risk, of the chemical detection system for arsenic.

TABLE V. Results of a Monte Carlo Simulation Run (5000 Individual Trials) of Lifetime Cancer Risks from 2 L/Day Water Consumption — Assuming that there is No Uncertainty in the Cancer Potency of Arsenic[A]

Data Set	50th Percentile (median)	Arithmetic Mean	95th Percentile
MIRA Water			
Bromoform	1.6E-6	5.1E-6	2.0E-7
Chloroform	2.0E-8	1.0E-7	3.8E-7
Dibromochloromethane	5.2E-7	1.8E-6	7.0E-6
Bromodichloromethane	9.9E-7	3.8E-6	1.4E-5
Subtotal all trihalomethanes	2.4E-6	5.7E-6	2.0E-5
DEHP	1.0E-7	4.3E-7	1.8E-6
Subtotal, all organics	2.8E-6	6.1E-6	2.0E-5
Arsenic	8.1E-5	8.1E-5	9.6E-5
Total	8.6.E-5	8.7E-5	1.1E-4
AWT Water			
DEHP	2.0E-7	8.2E-7	3.2E-6
(Arsenic)[B]	*5.6E-6*	*6.3E-6*	*1.7E-5*
Total	6.3E-6	7.2E-6	1.9E-5

[A]Differences between Tables IV and V for chemicals other than arsenic reflect statistical sampling fluctuations between different simulation runs of 5000 trials each.

[B]Caveat: Arsenic is not present in AWT water in amounts that are detectable with any confidence or reliability. These results are shown to illustrate the limitations, in terms of overall risk, of the chemical detection system for arsenic.

dependent on an innovative procedure we used to assign uncertainties to cancer potency estimates from both human data (e.g., arsenic) and animal projections, as well as our analytical uncertainties in the average amounts of contaminants present. If the human-derived arsenic cancer potency value is treated as a point estimate — having no uncertainty — the estimate of the mean risk for the MIRA water falls to 0.9 cancers per 10,000 people.[B] (The mean risk estimate falls when uncertainty is removed from the calculation because the uncertainty distribution is assumed to be highly skewed (see Figure 2) with a mean that is considerably larger than the single most likely value.) Regardless of which of these estimates is deemed most appropriate for policy-making purposes by the City of San Diego, the indicated risk is not negligible (under California's Proposition 65 standards, the criterion for a de minimis risk is 0.1 conservatively estimated cancers per 10,000 people), although it is not as large as the largest environmental risks that have been identified to date (e.g., lung cancer from radon progeny in houses and from environmental tobacco smoke).

"By contrast, the water that we sampled from the AWT system does not have enough arsenic to be reliably detected. Nevertheless, our risk calculations indicate that even if we make the assumption that arsenic is, in fact, present at levels that, due to analytical insensitivities, might be present, the AWT water poses a mean risk that is tenfold lower than the MIRA water. If we base the risk assessment for the AWT water only on those chemicals that were reliably detected, the indicated mean estimate of lifetime risk is slightly less than 1 cancer per 1 million people."

Conclusions and Caveats

The extended example above illustrates that it is possible to provide some expanded insight into the range of "not clearly incorrect answers" for risks, taking into account multiple sources of uncertainty, and without a great deal more work than is usually done in more conventional "screening"-type risk analyses, such as those currently done for Superfund sites. Of course, the present analysis could have benefited from a far more systematic study of uncertainties for individual cancer potencies in the light of specific toxicological information for particular chemicals, a more adequate representation of the delivered dosage of water contaminants due to multiple routes of exposure from water (e.g., dermal, inhalation), and some other factors. Nevertheless, we feel that this level of analysis does offer some improvements in the information provided to decision-makers for a modest increment in analytical efforts.

Of course, no analysis of the combined effects of multiple sources of uncertainties can be better than the accuracy of the individual estimates of component uncertainties that are fed into the simulation. Arriving at appropriate descriptions of these component uncertainties is by no means a trivial task. In this regard, we have previously offered[11] three tongue-in-cheek "laws" of uncertainty/variability analysis that should inject a final note of the need for due skepticism here.

1. Nearly all distributions look lognormal, as long as you do not look too closely. (One is, therefore, well advised to reason carefully about the likely causes of uncertainty or variability in specific parameters and whether this suggests a particular distribution is appropriate.)
2. Any estimate of the uncertainty of a parameter value will always itself be more uncertain than the estimate of the parameter value. (For example, fluctuations in individual data points will generally have a greater influence on the estimate of a standard deviation than on the estimate of the mean of the parameter.)
3. The application of standard statistical techniques to a single data set will nearly always reveal only a trivial proportion of the overall uncertainty in the parameter value. (This is because systematic error among data sets is generally much larger than random error within data sets.)

[B] A more conventional calculation, utilizing simply the basic EPA cancer potency factors without modification, yields a lifetime risk of about 1.3 cancers per 10,000 people. These cancer potency factors are something of a mixed group, in that implicitly the arsenic and benzene values, derived from human data, are central tendency values, whereas the potency estimates derived from animal data (e.g., chloroform) are upper confidence limit values.

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Current Applications of Chemical Risk Assessment within Military Environments

Use of Risk Assessment in Evaluating Remediation of PCBs

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Risk assessment is often used to evaluate the need for, and the potential effectiveness of, remediation of chemical contamination. Estimating the potential residual risk from polychlorinated biphenyls (PCBs) may involve more complex issues than many other chemicals; the presence of more decision points in a risk assessment results in more potential for variation among the analyses performed by different people. For example, the toxicity of PCBs is known to vary with composition, but methods for estimating the toxicity of these complex mixtures for different toxicity endpoints are controversial. Changes in composition of the mixture with time, medium, and place of exposure may also significantly alter the toxicity and concomitant risk. In addition, some of the more interesting potential routes of exposure (e.g., contact with contaminated surfaces) may be estimated using a variety of models and assumptions, resulting in substantially different assessments of exposure and risk. Although various complex factors should be considered in the risk assessment, simple models should also be used to estimate an upper bound on risk to ensure that a concatenation of conservative assumptions do not result in impossible situations (e.g., predicting exposure to more PCBs by one or several routes than were available for the exposure that was estimated).

Introduction

Documents on risk assessment techniques, guidance manuals, and values for assumptions are numerous. Scientists involved with risk assessment of certain chemicals, including polychlorinated biphenyls (PCBs), face an additional abundance of references on the particular properties and concerns of those chemicals. As it is impossible to cover all aspects of risk assessment of PCBs in any short paper, this discussion will focus on three issues: 1) differences in the toxicity of various PCB mixtures; 2) changes in the composition of a particular mixture of PCBs as a function of time, location, and medium; and 3) necessity of "reality checks" on risk assessments, especially involving PCBs, as illustrated by PCB–contaminated surfaces.

Toxicity of PCB Mixtures

Evaluation of the toxicity of PCBs is complicated by the historical practice of testing PCBs as mixtures, primarily the commercially available mixtures. Although in recent years some of the individual isomers have been examined for more than their ability to bind to receptors or induce enzymes,[1–3] many of the toxicity studies that form the basis for risk assessments of human health, including all of the human exposure and epidemiology studies, have evaluated mixtures of PCBs.

Differences in approach to the evaluation of mixtures of families of closely related chemicals by regulatory agencies, specifically the U.S. Environmental Protection Agency (EPA), will be more completely discussed in a separate report. Briefly, EPA generally does not use composition of a particular PCB mixture to differentiate the potential for that mixture to cause adverse effects,[4] despite the known differences in toxicity of commercially purchased mixtures.[2,5,6]

How much can this regulatory policy affect the estimation of risk? Consider that for the individual isomers of a similar group of closely related compounds, polychlorinated dibenzo-*p*-dioxins, the carcinogenicity of individual isomers is assumed to vary by over 10,000-fold, and some are considered noncarcinogens for purposes of regulatory risk assessment.[7] The cost of a 10,000-fold more extensive remediation would be enormous.

What other options are available for evaluating toxicity of a mixture of PCBs? Where a commercial mixture has been tested for a particular toxic endpoint, those data could be used for risk assessment of that (or a very similar) mixture. Environmental exposure, however, may be to PCB mixtures that differ significantly from commercial mixtures. In such cases, toxicity has often been estimated by comparison with the most similar commercial PCB. When a mixture is negative (or untested) for a particular toxic endpoint, however, it should not necessarily be assumed that this mixture has the same toxic properties as other mixtures. Data from several mixtures and individual isomers clearly demonstrate that not all PCBs are equally toxic for each endpoint.[1,2,3,8] When an untested mixture has some of the same isomers as a mixture that is positive for a particular endpoint, prudence may dictate an estimation of what could be an adverse outcome of exposure if the toxic properties of the untested mixture were similar to those of the tested mixture. This assumption of ability to produce similar adverse effects, however, must be

clearly presented not only in the hazard identification step of the risk assessment but also in all subsequent steps of the evaluation. Risk estimates from analyses that assume similar toxic effects among mixtures of closely related chemicals should be clearly differentiated from those that have primary data to be considered in the hazard evaluation step of their risk assessment.

For some toxic endpoints, data are available to examine the ability of predictive models based on mixture composition. EPA[9] is currently examining a method based on toxicity equivalence factors (TEFs) for estimating the comparative potency of PCBs. As will be discussed in a separate report, however, TEFs based on enzyme induction similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin do not appear to correlate with one endpoint, i.e., carcinogenic potency. Methods for extrapolating information on the relative carcinogenic potency of commercial mixtures of PCBs, for example, by percentage of chlorination, have also been considered.[6] Such an approach has the advantage of directly incorporating the available data from cancer bioassays but the disadvantage of not including differences in isomer toxicity (as all equally chlorinated isomers are assumed to be equivalently carcinogenic).

Exposure to Mixtures of PCBs in the Environment

If assessing the relative toxicity of commercial PCB mixtures for all significant endpoints were sufficient to characterize the potential hazards from exposures to PCBs, the task would be large but finite. In the environment, however, the composition of PCBs changes with time,[5,10,11] thus affecting the relative risk of the relevant exposure. In this discussion, two additional complications will be considered: 1) changes in the composition by route of exposure and 2) decisions on which routes of exposure should be combined for a risk assessment of any (hypothetical) individual.

Consider, for example, PCB-contaminated soils. When modeling volatilization of PCBs from the soil, the Henry's Law constant or vapor pressure for each PCB mixture or isomer can be used to estimate release into the air. These constants can vary by approximately 10-fold, with the less chlorinated PCBs more likely to enter the air.[4,12] Similarly, soil can act like a chromatography column for PCB mixtures.[13] Under the conditions modeled by Andrews and Hathaway,[13] the first PCBs (in this case, dichlorobiphenyls) to reach the receptor through groundwater will be the less chlorinated. Dermal contact with, or ingestion of, the PCBs that remain in the soil, therefore, must be to a comparatively higher chlorinated mixture. Thus, the relative potency of the PCB mixture by inhalation, contact with groundwater, and contact with soil may differ. A risk assessment that simply sums the PCB exposure by all of these routes will not reveal the potential differences in toxicity of PCB mixtures that vary in composition by medium and route of exposure.

Exposure to PCBs in groundwater modeled by Andrews and Hathaway illustrates another consideration for risk assessments of PCBs. Not only did they find that the PCB mixtures were quite unlike commercial mixtures when the PCBs reached the receptors, but for some conditions modeled, exposure would first occur centuries in the future. Again, even when estimating the risk to a theoretical, maximally exposed individual (MEI), it may not be appropriate to combine some routes of exposure (e.g., current inhalation of volatilized PCBs and subsequent contact with contaminated groundwater). Moreover, if the less chlorinated isomers enter the air for an extended period of time, would there still be sufficient dichlorobiphenyls to substantially contaminate groundwater, or would significant exposure to PCBs via groundwater be even more delayed because the majority of the dichlorobiphenyls entered the air? Even for shorter time periods, if the direction of groundwater flow and prevalent wind direction are in opposite directions, it may not be realistic to combine these exposures for even the MEI. The need for an accurate accounting of the material present is the focus of the example in the next section.

PCBs on Surfaces: Mass Balance and Other Reality Checks

Risk assessors may become so involved with the complexities of their endeavor that they may fail to notice when their calculations have exceeded a simple appraisal by common sense. Good environmental risk assessors, therefore, should examine the "forest" as well as the "trees."

Consider a risk assessment of PCB-contaminated surfaces. In general, two major exposure pathways are considered for this situation: dermal contact with contaminated surfaces and inhalation of volatilized chemical. This example is instructive because it not only involves some of the issues in risk assessment of PCBs discussed above but also because it includes other assumptions of interest, since contact with surfaces is a less well-studied exposure pathway. Only chemicals such as PCBs that can persist on surfaces would be considered for this exposure pathway, with the exception of acute exposures.

A very conservative risk assessment might assume that vaporization rates for all PCBs are as high as the most volatile component and that levels of PCB remaining in the surface material are as high as the most hydrophobic constituent. If such assumptions are used and an extended duration (e.g., a lifetime) is also assumed, the risk assessment that results from the modeling exercise may not only assume that an inappropriate mixture of PCBs would be present for exposure by a given route (based on the physical–chemical properties of different isomers of PCBs discussed above) but may also assume exposure to more PCBs than were available during the time of exposure.

Such an outcome may originate from many assumptions.

For example, some of the simpler fate-and-transport models assume an infinite source of the contamination, whereas the actual source of contamination may be exhausted in less time than the duration modeled. Although these problems may occur for other chemicals, the combination of the persistence of PCBs in the environment and conservative assumptions and models that may overestimate the transfer of PCBs between media tend to exaggerate the problem.

Before dismissing conservative modeling, however, it should be recognized that, under certain conditions, use of multiple conservative assumptions may be appropriate. For example, conservative assumptions for each exposure pathway could be used to ensure that exposure by no one pathway is underestimated and could result in an unacceptable risk.

Risk assessments for various routes of exposure using such assumptions, however, should not be added without ensuring (at a minimum) that the total exposure of the MEI does not exceed the amount of chemical available for that duration of exposure.

A critical consideration in the potential for exposure to PCBs contaminating surfaces is the "ink pad" effect. This paradigm comprises several useful concepts. First, it assumes a reservoir of chemical that will become available over time. Second, the concepts of transfer of PCB from contaminated surfaces to skin and from the then PCB-covered skin to clean surfaces (with analogy to an ink stamp) are both included. Third, the possibility of exhausting the reservoir of PCBs, either temporarily or permanently, is introduced. Finally, similar to an ink pad drying out with prolonged exposure to air, changes in composition of the chemical mixture in the reservoir and variations in the effectiveness of the source to transfer the mixture due to volatilization and the potential for exposure to PCBs in air are included.

The extent to which the contaminating chemical is in a reservoir (Table I) can dramatically affect the exposure assessment portion of the risk assessment.[14] If all of the chemical is in a very thin layer on the surface and the room has a reasonable air exchange rate, standard models will predict that most of the chemical will be volatilized and removed from the room within hours or days. If all of the PCBs are not on the surface, the rate at which they migrate to the surface must be evaluated, and exposure may be for a longer duration.

TABLE I. Some of the Factors Affecting Dermal Exposure to PCBs in a Reservoir in Walls and Other Surfaces

Amount of PCBs available for exposure per day depends on:
- Amount of PCBs diffusing to the surface.
- Percent volatilizing from surface into air.
- Redeposition to surface from skin or air.
- Removal from room by the building's air exchange or on skin, i.e., person leaving room.

Amount of PCBs available for exposure per (working) lifetime depends on:
- Total mass of PCBs in building.
- Permeability of reservoir material, i.e., amount that reaches surface per (working) lifetime.

TABLE II. Some Activity-Based Exposure Assumptions (The "Ink Pad" Effect)

Types of activities that result in contact with surfaces.
- Amount of skin in contact with surface for each type of activity.
- Number of contacts with PCB-contaminated surfaces.
- Number of contacts with uncontaminated surfaces or number of times skin is washed.
- Percent of PCBs transferred per contact (PCB-coated surface to skin; PCB-coated skin to clean surface).
- Concentration of PCBs on available appropriate surface for each modeled activity.

Modeling PCB migration to the surface requires additional data (or assumptions) and adds additional uncertainty to the risk assessment. A determination (or assumption) that only a small portion of the PCBs are available on the surface during any time period, however, limits the total amount of exposure by all routes for that time period. Thus, it may be reasonable to assume that all the surfaces do not have a constant concentration (i.e., an unlimited source) of PCBs. Similarly, the PCBs available on contaminated surfaces must be apportioned between dermal exposure and inhalation exposure after volatilization from surfaces. Although a mass-balance check (total available PCBs versus total PCBs from all routes of exposure) would seem to be an obvious procedure, its implementation may be complex, and it is frequently absent from analyses.

Within the constraint of the mass of PCBs that are available during a specific time period, volatilization can be modeled by various techniques. When the concentration in the air has been predicted (by either a dynamic or static model), exposure to an individual can be estimated using a series of assumptions, although sometimes controversial, that are bounded by physiologic constants. (The manner of selecting from among these assumptions may also be influenced by degree of risk aversion or policy considerations.)

In contrast with the assumptions used for exposure to air, many more of the assumptions needed to estimate risk from exposure to surfaces have been less well studied and, therefore, have greater uncertainty. The general equation for estimating dermal exposure to PCBs from contaminated surfaces includes some values that can vary substantially with the method used to model contact (Table II). To simplify the illustration presented here, other assumptions, for example, the amount of PCB absorbed through the skin, are assumed to be the same for all methods for estimating exposure, even though they also can be controversial (e.g., dermal absorption may vary with concentration for some chemicals). EPA[15] is in the process of evaluating assumptions associated with exposure via dermal contact.

At least three distinct approaches can be used for estimat-

ing exposure through dermal contact. The most traditional risk assessment approach is to model activity that might result in exposure (Table II). Because much of this information may vary by location and accurate data are usually not available, the resulting risk assessments may differ significantly depending on the values used. One of the first steps in estimating dermal exposure by this approach is to determine which activities result in contact with contaminated surfaces. Although all PCB-contaminated surfaces contribute to PCB concentration in the air, only some surfaces are accessible for dermal contact. All models for exposure by dermal contact with surfaces, except those that assume all surfaces are as contaminated as the most contaminated surface, will incorporate a measure of accessibility by techniques such as use of a weighted average concentration or by separately modeling each type of surface based on accessibility (e.g., floor, surfaces within reach, high surfaces, and ceilings). Determining which surfaces are accessible and how frequently per time period each type of surface is in contact with the skin is not trivial for most situations. Following the ink pad paradigm, the amount of PCB transferred from contaminated surfaces to clean surfaces during repeated contacts throughout the workday should also be estimated. Day-to-day variation in activity for one individual and variation among individuals may result in a complex matrix that will not easily reduce to a few, tractable exposure scenarios.

A second approach, useful for chronic exposures, is to assume that an equilibrium exists between the person's skin that would contact surfaces and the appropriately weighted average of the PCB-contaminated surfaces in the room. Assumptions in this case are fewer because the activities of a person do not need to be estimated. Although this approach might seem very conservative, a comparison with the activity approach suggests otherwise, especially if conservative assumptions (i.e., some version of "worst case") are modeled. As a simplistic example, assuming a 50% transfer of PCBs from contaminated surfaces and four contacts per day, the exposure modeled by the activities approach (assuming no removal from the skin and all other values constant) would be twice that of the equilibrium approach (i.e., $[4][0.5x] = 2x$, where x is the concentration on the surface). Depending on the extent to which the PCBs on the skin are assumed to be transferred to a clean surface or removed by washing, the estimated exposure from this aspect of the activities approach to modeling exposure may still exceed that of the equilibrium approach, depending on the other activity assumptions adopted. Nevertheless, it would seem unlikely that, for chronic exposures, the actual exposure would exceed the equilibrium model using the appropriately weighted surface concentration.

Finally, available data may provide a rough estimate for human exposure. For example, Christiani et al.[16] measured serum PCB levels in workers in a facility that had residual PCB-contaminated surfaces from previous activities. The workers were occupationally exposed to PCBs only through contact with contaminated surfaces and inhalation of PCBs volatilized from these surfaces. Limitations of any epidemiology study must be recognized. It can also be difficult to correlate serum PCB levels to potential for occurrence of adverse effects. The uncertainties in this exercise, however, may be no greater than modeling exposure through estimating activities. For situations in which the surface PCB levels are near or below the level reported in Christiani et al., these data may be a more accurate representation of exposure and potential risk (or, if the contamination is lower, an upper bound of the risk). At a minimum, they represent a reality check on any modeling exercise.

Parenthetically, review of the Christiani et al. study suggests an additional issue concerning risk assessment of this situation. Exposure through inhalation was considered negligible by the authors, presumably because the concentration in air was below the detection limit. Depending on the location of PCB contamination on surfaces and the assumptions used for estimating exposure by inhalation or dermal contact, air concentrations at the detection limit in this study (1[illegible] $\mu g/m^3$) could contribute to the risk. If, in a particular situation, highly contaminated surfaces were inaccessible (i.e., contributing to air concentrations but not significantly to dermal contact), the PCBs in air at the detection limit might have a higher estimated risk than that from contact with contaminated surfaces. Thus, when a chemical is estimated to be relatively potent and detection limits are relatively high, a risk assessment of exposure at the detection limit should be performed before an exposure pathway is eliminated due to inability to detect the chemical.

Conclusions

Risk assessment of PCBs poses two generic problems: 1) the chemical is actually a complex, often changing mixture of chemicals, which increases the complexity of evaluating toxicity and 2) PCBs persist in the environment, which complicates modeling of exposure. These factors also limit the availability of data needed for estimating risk. Thus, common sense and upper-bound risk assessments (reality checks) are useful in preventing a combination of seemingly reasonable assumptions from resulting in an unreasonable risk estimate.

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PCBs on Naval Vessels

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The following is the abstract of the presentation by Mr. Riegel. His paper is not available for publication at this time.

In April 1989, the Navy was surprised by the discovery of polychlorinated biphenyls (PCBs) in certain items aboard its ships. For example, some wool felt material used for acoustical damping and in gaskets was found to be impregnated with PCBs; they had been added by some suppliers without the Navy's knowledge in order to reduce flammability. These uses were discovered during work done on a submarine at the end of its life. Existing regulations were developed before these unusual applications became known and mainly address conventional uses like electrical transformers and capacitors. The Navy is working on this problem under the existing regulations but will also work with regulators as opportunities emerge to revise rules in order to reflect actual Navy experience appropriately. Revised rules should also be based on accurate assessment of risk to personnel and to the environment. Persons skilled in the techniques of risk assessment are encouraged to apply the Navy's experience in this matter, including results of environmental measurements in this particular situation, and to participate in the process of updating PCB regulations using the results.

Short-Term Exposure Guidelines for Emergency Response: The Approach of the Committee on Toxicology

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For over 40 years, the National Research Council's Committee on Toxicology (COT) has, on request, recommended emergency exposure guidance levels (EEGLs) and continuous exposure guidance levels (CEGLs) for chemicals of concern to the Department of Defense (DoD). EEGLs provide guidelines for military personnel operating under one-time, emergency conditions whose circumstances are peculiar to military operations and for which regulatory agencies have not set relevant standards. CEGLs are recommended for normal, long-lasting military operations. The guidance levels are set assuming that the military population is healthy and relatively young and includes women of child-bearing age. An EEGL is defined as a concentration of a substance in air that may be judged by DoD to be acceptable for the performance of specific tasks during rare emergency conditions lasting 1–24 hours. Exposure at an EEGL is not hygienic or safe; exposure at an EEGL may produce reversible effects that do not impair judgment and do not interfere with proper responses to an emergency. CEGLs are ceiling concentrations intended to avoid adverse health effects, either immediate or delayed, and to avoid degradation in performance of military personnel after exposures for as long as 90 days. Accumulation, detoxification, and excretion are important factors in determining CEGLs. For a substance that has multiple toxic effects, all the adverse effects — including reproductive and developmental effects; cancer; and neurotoxic, respiratory, and organ-specific effects — are evaluated and the most seriously debilitating, work-limiting or sensitive one is selected as a basis for guidance. Occasionally, DoD asks COT to recommend a short-term, public emergency, exposure guidance level or SPEGL. A SPEGL is defined as an acceptable peak concentration for unpredicted, single, short-term, emergency exposures of the general public. SPEGL's are generally set at 0.1 to 0.5 times the EEGL to provide appropriate safety factors for the wide range of susceptibility in the general public.

Introduction

For over 40 years, the Committee on Toxicology (COT) of the National Research Council (NRC) has, upon request, advised the Department of Defense (DoD) on the ceilings for exposure to airborne chemicals of interest to DoD under emergency exposure conditions. The levels are intended as guidance for single emergency exposure conditions (i.e., an occurrence expected to be infrequent in the lifetime of a person). The levels are not intended for conditions that are to be repeated on a regular basis. The guidance levels are for military personnel operating under emergency conditions whose circumstances are peculiar to military operations. The guidance levels should never be considered as standards for the general population. Under some circumstances, DoD asks COT for guidance levels for short-term emergency exposures that may affect the general public. Such guidance levels are for one-time, single exposures under emergency conditions and are adjusted for the difference in the population of the general public compared to the military. Finally, COT also provides, upon request, guidance levels for continuous exposures (up to 90 days) of military personnel in atmospheres specific to military operations (e.g., submarines). NRC has published seven volumes giving recommended guidance levels for 37 chemicals.[1–7]

In the following sections, the different guidance levels provided to DoD by COT will be defined and described in more detail. The process of developing the guidance levels will be reviewed, and example compounds will be used to illustrate that process.

Definitions

The Emergency Exposure Guidance Level (EEGL) is a concentration of a substance in air that may be judged by DoD to be acceptable for the performance of specific tasks during rare emergency conditions lasting 1 to 24 hours. The EEGL should allow personnel to continue to perform tasks necessary to take care of the emergency conditions and to allow self-rescue. Therefore, the EEGL should not impair judgement, interfere with performance of tasks in response to the emergency, nor cause irreversible harm to the personnel. The EEGL may, however, cause transient adverse effects, such as increased respiration rate, headache (but not debilitating headache), mild central nervous system effects, or irritation to the eyes or upper respiratory tract. An EEGL is acceptable only in an emergency, when some discomfort or risks must

be taken to avoid greater risks, such as fire, explosion, or massive releases of toxic material.

The calculation of an EEGL is based on the exposure population being military personnel who are healthy and relatively young. Women are included; thus, the potential fetotoxicity of the exposure material is considered. Personnel are expected to have appropriate protective equipment available and to have planned escape routes, but EEGLs are not based on the availability of the protective equipment or the escape routes.

The Short-Term Public Emergency Guidance Level (SPEGL) is a suitable concentration for single, short-term, emergency exposure of the general public. The SPEGL is developed at the request of the DoD for emergency situations in which the public might be involved. The SPEGL considers sensitive populations, such as children, the aged, and persons with serious, debilitating diseases.

The Continuous Exposure Guidance Level (CEGL) is a ceiling concentration designed to avoid adverse health effects, either immediate or delayed, of more prolonged exposures and to avoid degradation in crew performance that might endanger the objectives of a particular mission as a consequence of continuous exposure for up to 90 days. Thus, CEGL is not a short-term, emergency guidance level but is included in this report because it is usually calculated based on some fraction of the EEGL. The CEGL is intended to provide guidance for military operations lasting as long as 90 days, such as in submarines.

Process for Developing Guidance Levels

COT has published a summary of the procedures used in recommending guidance levels for DoD.[8] The first step in developing guidance levels requested from DoD is to search the literature for information on the toxicology of the substance of concern. It is essential to gather basic information on the chemical and physical properties of the substance to understand how the material will act in an emergency situation. What will its physical form be in the atmosphere? Will it be stable or break down rapidly? How will its solubility affect its retention in the respiratory tract? How will its particle size influence deposition in the respiratory tract?

Next, the literature is searched for any indication of acute toxic effects and the concentrations that induce those effects. The most valuable information is that which is based on human responses to the substance. Studies indicating the effect of the compound on the ability of humans to perform difficult mental or physical tasks are especially useful. In the absence of human data, acute responses of animals to the substance are used. All types of acute toxicity data are considered, including reproductive and developmental toxicity, neurotoxicity, respiratory toxicity, and other organ-specific effects.

If the compound has been shown to be a carcinogen, a risk assessment is used that is based on a linearized, multistage model[9] to provide an estimate of an exposure that would not lead to an excess risk of cancer greater than 1 in 10,000 exposed persons. Pharmacokinetic information is also sought in the search of the literature. The ability of the body to clear the inhaled substance is of concern in setting the CEGL based on the EEGL (i.e., in going from an acute exposure situation to a chronic exposure scenario). The ability of the body to clear the substance is also of concern in estimating the potential for a short-term, emergency exposure to cause an effect such as cancer.

In addition to the search of the literature for toxicity information, COT draws up a list of all other exposure limits that have been set for the compound by any agency. Such a list provides information that allows the Committee to judge if its deliberations are in reasonable accord with the recommendations of other groups of experts who have evaluated the same compound. The purpose of this comparison is not to mimic the regulatory levels set by others but to determine if the COT deliberations resulted in guidance limits that are reasonable in light of the special needs of the military. It should be emphasized that the guidance levels recommended by COT are not like standards issued by regulatory agencies and must not be so construed. They are intended for use by DoD exclusively for its particular exposure situations.

Based on the information gathered from the literature, COT recommends an EEGL. For a substance that has multiple toxic effects, COT chooses the effect that is most debilitating or most likely to interfere with performance in an emergency situation as the basis for the EEGL. A safety factor of 10 is used (i.e., the EEGL is reduced by one-tenth) if only animal data are available or if the data are from a route of exposure that is different from the expected route in the emergency. The EEGL based on acute toxic effects is then compared to the level of the compound that would be recommended based on the cancer risk assessment process. The lower number is recommended as the EEGL.

Usually, the 1-hour EEGL is calculated first, and the 24-hour EEGL is then set based on Haber's Rule, which states that exposures having the same concentration times time constant will cause equivalent toxicity. Based on this rule, a 24-hour EEGL would be approximately 1/24th of the EEGL for 1 hour. For some compounds, such as irritant gases, for which the concentration is the major parameter determining toxicity, Haber's Rule is not followed, and the EEGL for 1 hour may be the same as for 24 hours.

For some compounds, DoD may request COT to recommend a SPEGL. Because the public may include some sensitive subgroups that are not in the military, such as severely debilitated persons, young children, and the very old, the recommended SPEGLs are lower than the EEGLs. Usually, the SPEGLs are 0.1 to 0.5 times the EEGLs. A safety factor of 2 is used to protect sensitive subgroups in the population. If newborns or fetuses are to be protected, a safety factor of

10 is used.

Likewise, DoD sometimes needs recommendations for CEGLs or ceiling levels for continuous exposures in specific military operations. The CEGL is usually 0.01 to 0.1 times the 24-hour EEGL. If the substance clears from the body rapidly or is quickly detoxicated, a safety factor of 10 may be used. If the compound is expected to accumulate in the body or is only slowly detoxicated, than a safety factor of 100 or even higher may be used.

Example Compounds

Benzene

The basis for COT's guidance levels for benzene is described in Volume 6 of the series of documents published by the NRC/COT.[6] A brief description of that process will serve as an example of the approach used by COT.

Acute exposures to high levels of benzene are known to produce central nervous system (CNS) effects that could be debilitating. Chronic exposure to lower levels of benzene is associated with hematotoxicity and acute myelocytic leukemia. A review of the literature indicated that humans exposed at 50–150 ppm benzene for 5 hours complained of headache, lassitude, and weakness, whereas exposure at 25 ppm for 8 hours had no effect.[10] Subacute hematotoxicity was induced in workers exposed at 25–100 ppm benzene over 10 years.[6] Chromosomal aberrations in peripheral white blood cells were observed in workers exposed to as little as 1 ppm benzene for over 1 year.[6,11]

Animal studies indicate that exposure of rats at 1–10 ppm benzene for 6 hours results in an increase in chromosomal aberrations in bone marrow cells.[12] Fetotoxicity has been observed in rats exposed at 50 ppm benzene for 7 hours/day during days 6 through 15 of gestation, and teratogenicity resulted if the exposure was at 500 ppm.[13]

The current Occupational Safety and Health Administration (OSHA) regulations for benzene allow an 8-hour, time-weighted average (TWA) exposure of workers to 1 ppm benzene with a ceiling exposure limit of 5 ppm (15-minute TWA).

Based on the above information, COT set the EEGLs based on acute CNS symptoms in humans. Exposure at 50 to 150 ppm for 5 hours caused headache, lassitude, and weakness, but exposure at 25 ppm for 8 hours produced no observable CNS effects. Therefore, exposure at 50 ppm for 1 hour can be expected to have mild, but not incapacitating effects. Thus, COT set the 1-hour EEGL at 50 ppm benzene and the 24-hour EEGL at approximately 1/24 that value or 2 ppm.

However, benzene is a probable human carcinogen; therefore, COT evaluated the exposure to benzene that would not allow an excess cancer risk above 1 in 10,000. To calculate this value, COT accepted the EPA Carcinogen Assessment Group's report that an excess risk of cancer for lifetime (70 years) exposure to benzene at 1 ppb was 24×10^{-6}.[14] To convert to the level of benzene that would cause an excess cancer risk of 10^{-4}, the COT calculated:

$$\text{Risk of } 1 \times 10^{-4} = \frac{1 \times 10^{-4}}{24 \times 10^{-6}} \times 1 \text{ ppb} = 4.2 \text{ ppb}$$

To convert from a 70-year exposure to a 24-hour exposure, the following calculation was made:

$$4.2 \text{ ppb} \times = \frac{70 \times 365 \text{ days}}{2.8 \text{ (multistage factor)}} = 30{,}015 \text{ ppb or } 38 \text{ ppm}$$

The multistage factor is based on the work of Crump and Howe[9] to allow for possible variability in the stage of the cancer process at which benzene or its metabolites act. Therefore, based on the carcinogenic properties of benzene, the 24-hour EEGL would be 38 ppm, and the 1-hour EEGL would be 24 times as high, or 912 ppm.

Because the EEGLs based on acute toxicity were lower than the EEGLs that would be set based on benzene as a carcinogen, the acute toxicity data were used to set the 1-hour EEGL at 50 ppm and the 24-hour EEGL at 2 ppm.

Hydrogen Chloride

An example of a chemical that does not follow Haber's Rule is hydrogen chloride (HCl). The irritancy of this gas is more associated with its concentration in air than with the time of exposure. Therefore, the 1-hour and the 24-hour EEGLs for HCl are both 20 ppm, and the 1-hour and 24-hour SPEGLs are both 1 ppm.

The 1-hour SPEGL for HCl can be compared to that recommended by industry as a Level 1 Emergency Response Planning Guideline (ERPG) that is used in planning for responses to emergency situations in the chemical industry.[15] This guideline is defined as the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing anything more than mild, transient, adverse health effects or perceiving anything more than a clearly defined objectionable odor. The ERPG Level 1 is set at 3 ppm. The difference between the ERPG and the SPEGL lies in the people the guideline is meant to protect. The SPEGL considers sensitive subpopulations, whereas the ERPG only considers "nearly all individuals."

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Three-Tier Approach to Chemical Spill Response

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Major chemical spills create special problems in protection of both public and worker health. The current standard of practice for a major spill requires the evacuation of personnel for a specified distance downwind, using exposure limits and dispersion models to define a toxic corridor's safe and unsafe areas. The implication of this practice is that there is significant health risk inside the toxic corridor and no significant risk beyond the corridor. Because of the high level of uncertainty in both the exposure limits and the dispersion modeling used, these corridors are understandably conservative in an attempt to develop a high degree of confidence that people outside the toxic corridor are not endangered. However, this conservative practice can result in very large, predicted, toxic hazard corridors creating evacuation problems and additional hazards.

Before 1985, the United States Air Force used National Academy of Science (NAS) – National Research Council (NRC) published emergency public exposure limits for nitrogen dioxide (NO_2) and the hydrazine fuels used in rocket and missile operations. In 1985 and 1989, the NAS–NRC Committee on Toxicology published a new, lower, short-term public exposure guidance level (SPEGL) for NO_2 and the hydrazines used in Titan rockets. This lowering of the exposure limit caused a significant increase in the length of the predicted potential toxic corridor at Vandenberg Air Force Base, extending it well beyond the controlled areas of the base into populated areas, significantly impacting the base's ability to perform higher risk operations such as fueling and launching the rocket. This forced a re-evaluation of the standards and practices used for hazard planning.

Predicting the toxic hazard corridor requires three principal elements: rate of contaminant evaporation, dispersion modeling, and exposure limits. This paper focuses on the exposure limits, the associated health risk, and response actions.

If a chemical release does occur, the information needed by the Base Commander is the degree of risk to human health and safety. Risks can be either immediate or long term and can affect the general population or selected sensitive individuals.

In the case of NO_2, there is much experience with human exposure. In the average population, the risk is considered immediate with a finite threshold for irreversible health damage; however, there is a sensitive subpopulation that may suffer from secondary effects caused by exposures at much lower levels. The SPEGL is set at a level to protect this sensitive subpopulation, but it does not give the Base Commander the risk information needed to evaluate, plan for, and respond to a large chemical spill. The Environmental Protection Agency's (EPA) *Technical Guidance for Hazard Analysis, Emergency Planning for Extremely Hazardous Substances* (December 1987) sets the "Level of Concern" for public emergency exposure at 1/10 of the "Immediately Dangerous to Life and Health" (IDLH) level. EPA has also established an air pollution ceiling goal for NO_2, above which is the "significant harm level" for the public as a whole, including sensitive subpopulations. The Occupational Safety and Health Administration (OSHA), the American Conference of Governmental Industrial Hygienists (ACGIH), and the National Institute for Occupational Safety and Heaith (NIOSH) have all published occupational exposure limits for short-term, periodic exposures.

The hydrazine family of fuels creates a different problem. Although acute toxicity data are available, these chemicals have been listed as suspected human carcinogens. This identification as suspected carcinogens caused NIOSH to remove the IDLH listing for these chemicals from the NIOSH *Pocket Guide to Chemical Hazards*, Fifth Printing. The Pocket Guide data were not intended to be used for emergency response; however, the Guide had become the standard source for IDLH data from a recognized agency. Therefore, when the IDLH levels for suspected carcinogens were deleted, a void was created in "officially recognized" IDLH values for hydrazines. This makes it difficult for a Base Commander to defend the use of an exposure limit that is not sanctioned by a recognized agency.

In order to provide the Base Commander with better tools to evaluate risk from and respond to failures of these fuel systems, we developed a risk-based approach to toxic hazard prediction and response. The approach identified three risk categories, each with an associated risk and response procedure. Although this approach may not be necessary or practical for small chemical spills, it greatly helps manage both planning and response to large toxic chemical spills.

Table I shows the sources of several published exposure limits for the primary rocket fuels. This information was used to identify existing standards and to help clarify relative risks for different exposure limits. These risks can be divided into three categories: immediately hazardous to life and health,

TABLE I. Exposure Standards and Levels of Concern (L.O.C.)

Standards		Level /Tier		
		1	2	3
Nitrogen Dioxide				
IDLH/1/2 IDLH	50/25 ppm	X	—	—
EPA L.O.C.	5 ppm	—	X	—
EPA significant harm level/	2 ppm (1 hr avg.)	—	—	—
pollution ceiling goal	0.5 ppm (24 hr avg.)	—	—	—
SPEGL/NAS–NRC	1 ppm (1 hour)	—	—	X
ACGIH short-term exposure limit (STEL) (1990)	5 ppm (15 min)			
OSHA STEL	1 ppm (15 min)			
UDMH (Unsymmetrical dimethylhydrazine)				
IDLH/1/2 IDLH	50/25 ppm	X	—	
EPA L.O.C.	5 ppm	—	X	
SPEGL/NAS–NRC 1989 (cancer)	24 ppm (1 hr)	—	—	
ACGIH time-weighted average (TWA), (1990) [proposed]	0.5 ppm [0.01 ppm]			
OSHA STEL	0.5 ppm (15 min)			
Hydrazine				
IDLH/1/2 IDLH	80/40 ppm	X	—	
EPA L.O.C.	8 ppm	—	—	
SPEGL/NAS–NRC 1989 (liver)	2 ppm (1 hr)	—	X	
ACGIH TWA (1990) [proposed]	0.1 ppm [0.01 ppm]			
OSHA STEL	0.1 ppm (15 min)			

Control to this limit required for planned and repetitive releases.

without regard to long-term cancer risk; potentially hazardous to the general public with effects being reversible or minor; and not significantly hazardous to the general public but posing increased risk to a sensitive subpopulation.

Table II defines the levels of concern categories and reflects the recommended response action for each level of risk. In addition, Table I indicates which exposure limit best fits each level of concern.

This approach requires that the Base Commander accept a certain level of risk for public exposure potential by using exposure hazard data that are available but not "officially" sanctioned; yet, it allows the Commander the flexibility to conduct hazardous operations with a high level of confidence that an effective response can be made to a major chemical release.

Implementation of the three-tier approach required an education campaign for the commanders and operators to get them to understand and accept this new way of planning for disaster. Commanders had to accept the uncertainty of not having a "national standard" to rely upon. Operating instructions, disaster response plans, and computer dispersion models had to be modified to deal with levels of risk and three levels of toxic corridors.

In the final analysis, however, this three-tier approach to managing hazardous chemical spills provides the operational commanders with a risk management tool that permits increased flexibility in establishing policies and in managing hazardous operations with a higher level of confidence.

TABLE II. Description of Levels of Concern

Level 1: Control Access and Evacuate

Immediately dangerous to life and health. Concentrations pose significant risk to exposed personnel.

Recommended Action: Evacuation should be performed unless it creates more risk than seeking shelter or remaining in air-tight shelters.

Level 2: Seek Shelter or Evacuate

Exposure poses some risk to the average individual.

Recommended Action: Seek shelter indoors with outside air intakes closed or evacuate, depending on situation and duration.

Level 3: Sensitive Individuals

Exposure poses no hazard to normal and healthy individuals. Certain sensitive individuals (asthmatics and certain other lung-diseased people) may be at some risk if exposed.

Recommended Action: Similar to Stage 3 air pollution alert, notify the public of release, provide information on potential public exposure and effects, and advise sensitive individuals to avoid strenuous physical activity, remain indoors, and close air intakes. Applies only to N_2O_4/NO_2.

Developmental Medical Research on Liquid Gun Propellants

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A research program is described that addresses exposure and health effects potential for a future liquid propellant artillery system. The principal focus of the study is the prediction of health effects based upon hypothetical weapons system combat and training scenarios. Accidental spills of the liquid propellant are expected to be the principal mode of exposure. The swine dermal model is the principal assay used for identifying health effects arising from accidental spill situations. The study was initiated by the development of procedures for collection of data on humans accidentally exposed during the weapons system research and development phase. This information, as well as information from completed toxicology studies, was shared with industry and government participants for worker protection and for the development of a medical surveillance plan. System description scenarios were developed at an early stage in order to integrate human exposure data and animal toxicology studies into assessments of potential risks. Subsequent updates to these scenarios often led to changes in the toxicology studies in an iterative fashion.

Liquid Propellant 1846 consists of 61% hydroxylammonium nitrate, 19% triethanolammonium nitrate, and 20% water. Previous studies of this material have demonstrated significant dermal injury potential, including sensitization, irritation, and following extended exposure, marked necrosis. Dermal exposure is followed by methemoglobin increase. The results of recently completed and ongoing toxicology studies are described. Study protocols designed to simulate weapons systems scenarios with the swine model are also discussed. These protocols include assessing levels of relative exposure (accidental spill potential), water rinsing of dermal and ocular surfaces, and absorption by clothing. Data requirements to complete a health effects risk assessment for Army decision-makers are listed and discussed.

Introduction

Liquid gun propellant (LP) is the basis for a radically new approach to artillery propulsion systems. The propellant can be metered into the combustion chamber to achieve unique combinations of firing rate and range that cannot be accomplished by traditional artillery systems. LP is expected to offer major advantages over solid propellants due to significant reductions in production and transportation costs, higher storage quantities in combat vehicles, and reduced vulnerability to accidents or enemy fire.

Over the past decade, several formulations for LP have been considered. The most recent formulation, LP1846, will be used if the U.S. Army elects to continue development of LP artillery systems. LP1846 is composed of hydroxylammonium nitrate (HAN), triethanolammonium nitrate (TEAN), and water in the ratio 60.8:19.2:20 volume to volume (v/v) HAN:TEAN:water. The molecular structures of HAN and TEAN are shown in Figure 1.

The U.S. Army Biomedical Research and Development Laboratory (USABRDL) is currently assessing the health risks associated with LP1846. The results of this assessment will be used in the basic program decisions concerning whether to continue with the development of LP systems. To be considered in the decision-making process are documented human accident scenarios, medical surveillance data from exposed persons, results of toxicity studies, analysis-of-use scenarios, and construction of hypothetical exposure scenarios. The medical research plan governing the direction of this assessment focuses on health risks faced by soldiers in combat and training. The risks encountered in production facilities will be addressed at a later time. This priority was based 1) on the recognized higher incidence of combat accidents that could lead to exposure and 2) on the lower potential for engineering design to provide protective measures in combat and training scenarios, as compared to production facilities.

Study Design

Several key or unique elements of the study were designed to address the objectives described above. There was a strong interest in maximizing the working relationship between the weapons developer and the Army medical community. As the weapons design evolved, potential routes and frequency of exposure from different operating scenarios were examined. In turn, the results from medical studies influenced system design. A medical surveillance program involving civilian contractors and Army medical facilities was initiated at an early stage. This program emphasized the

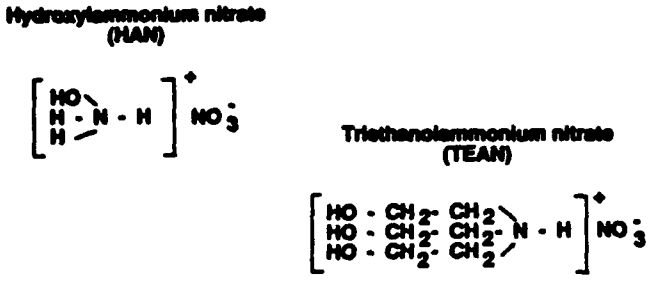

FIGURE 1. Components of liquid gun propellant.

rapid reporting of surveillance results and accidents in order to build a database on human exposure. Protocols for surveillance were standardized and health effects data shared in order to ensure that the information concerning the potential health effects of LP was disseminated promptly to medical personnel and that accident response procedures were current and appropriate. In the approximately 4 years that the medical surveillance program has been in operation, several revisions to the guidelines, safety procedures, and Material Safety Data Sheets were made.

The principal toxicology studies were designed to mimic potential field exposure(s) as closely as possible. The toxicity of LP1846 is due primarily to HAN, the major ingredient. HAN readily dissociates into hydroxylamine and free nitrate at neutral pH, and as expected, some of the health effects of LP1846 (i.e., severe skin injury and methemoglobin formation) are similar to those of hydroxylamine. Because accidental spills were judged to be the most serious threat, the most recent studies have concentrated on effects associated with skin contact. Swine were chosen as the experimental animal for these studies because they are considered to be a good dermal penetration model for human skin.[1] Studies are in progress with swine to evaluate the effects of repeated exposure, washing exposed skin, and exposure to saturated clothing. Other studies were designed to evaluate the systemic effects of LP1846 and to determine the risk that LP1846 would represent to the soldier when exposures occurred by routes that are most likely to occur on the battlefield.

Human Exposure and Medical Surveillance

Although documented reports of human contact with LP are limited, it is known that skin contact with LP can cause an immediate, transient sensation of burning and the appearance of skin lesions within 24 hours. In one medical report, a worker wiped his arm across a metal fixture wetted with LP1846. Later in the day, a macular papular rash developed in the area of contact. His physician prescribed a pHisoHex® wash followed by a cortisone cream; the rash resolved within a week.

Other medical reports indicate that removal of LP by rinsing with water can prevent or reduce the seriousness of skin lesions. Two individuals became contaminated with LP on the front of the pants and hands in an incident that involved a spill of approximately 1.5 L of LP. In both cases, the men washed their hands with distilled water within 20 seconds and changed their clothing within 3 hours. Medical examination on the following day revealed no signs or symptoms related to the spill.

A final medical report suggested that LP can cause an allergic sensitization. In this particular case, the affected individual routinely worked in the laboratory with small quantities of 13 M HAN. When she worked with both HAN and α,α- dipyridil, she developed an allergic-type reaction to seafood that disappeared when she was not working with these substances. She eventually developed a rash on the fingers of her hand, leading to papules and vesicles, which became a tense blister. This rash was thought to represent an allergic response to HAN. In addition to this case, there are several anecdotal reports which suggest that HAN may be a sensitizer. Although the evidence for this is largely circumstantial in humans, it is known that hydroxylamine is a potent sensitizer in humans and animals.[2] As reported below, LP1846 has been shown to be an effective sensitizer when applied topically to guinea pigs.

In the 4-year period during which a cooperative U.S. Army/industry medical surveillance program has been active, medical surveillance tests have not reported any increases in methemoglobin values because of LP exposure. However, few exposures were followed up with blood tests. Recent data indicate that the time of blood collection in relation to the time of exposure is important.[3] Thus, some cases of elevated methemoglobin could have been missed if the blood was not examined at the time maximum methemoglobin levels would be expected. This is especially important in cases where individuals washed exposed areas within several hours after exposure.

Toxicology

Interest in the toxicity of LP began in the early 1980s. At that time, studies with the earlier formulation LP1845 (63.2:20.0:16.8 [v/v] HAN:TEAN:water) began at the U.S. Army Environmental Hygiene Agency (USAEHA). Because HAN is the major contributor to the health effects of LP, and because the formulations of LP1845 and LP1846 are quite similar, all three are being considered in the assessment of the health risks associated with the current LP formulation. A brief summary of studies conducted with these formulations is given below.

Genotoxicity

HAN was tested by the *Salmonella*/Ames assay with and without metabolic activation systems in five tester strains. It was negative in all cases.[4] Similarly, HAN was not mutagenic in the mitotic gene conversion assay with *Saccharomyces cerevisiae*. A test for the dominant lethal effect,

TABLE I. LD_{50} Values of HAN in Rats, Rabbits, and Mice

Species	Route	Sex	LD_{50} (mg/kg)
Rat	Oral	M	822
Rat	Oral	F	520
Mouse	Oral	M	810
Rat	Intraperitoneal	M	148
Rat	Intraperitoneal	F	187
Rabbit	Oral	M	101
Rabbit	(unoccluded) dermal	M	70
Rabbit	Intravenous	M	37

Data from Asaki et al.[11] and Metker et al.[12]

performed in CF-1 mice, revealed no evidence of genetic damage to the sperm that could affect either fertility or survival of the fetus.[5] TEAN is also negative in the Ames *Salmonella* assay.[6]

LP1846 was negative in an *in vitro* rat hepatocyte DNA repair assay (unscheduled DNA synthesis)[7] and the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) assay.[8,9] Results of tests of the clastogenic potential of LP1846 in CHO cells[10] were considered to be inconclusive because only the highest dose tested induced chromosomal aberrations. The results were further confounded by the low pH of the final cell suspension because pH extremes can cause chromosome breaks.

Acute Effects

The toxicity of HAN varies markedly among different species; the oral LD_{50} is nearly an order of magnitude lower in rabbits than in rats (Table I).[11,12] LD_{50} studies in rabbits also showed that HAN is equally toxic by dermal and oral exposure.

LP is a strong skin and eye irritant. Introduction of LP1846 into rabbit eyes produced iritis, conjunctival redness, chemosis, and corneal opacities that lasted for up to 1 week. Washing the eye 30 seconds after application of LP1846 eliminated the corneal opacity and reduced the duration and severity of the iritis, chemosis, and conjunctival redness. Washing at 10 seconds after application further reduced the severity and duration of these symptoms, but signs of ocular irritation were still present.[13,14]

Sensitization

HAN[11,13] and LP1846[8] were tested in standard skin sensitization studies in Hartley guinea pigs. Negative results were obtained when 0.1% HAN was administered by intradermal injection. However, positive results were obtained when animals were treated topically with undiluted LP1846. The latter results are in accord with reports described above of allergic contact dermatitis in humans exposed to LP. The sensitization brought about by LP1846 may be related to the presence of hydroxylamine, a potent skin sensitizer in humans and animals,[2] and to triethylamine, which has also been reported to be a skin sensitizer.[15]

Systemic Effects

Oral Exposure: Single Dose

The primary known systemic effect of LP is the production of methemoglobin which appears in the blood soon after oral, inhalation, or dermal exposure. Studies in beagle dogs demonstrated that methemoglobin becomes elevated rapidly after ingestion of LP1845, HAN and hydroxylamine hydrochloride[12,16] (Figure 2). Methemoglobin increased to approximately 50% within 1.5 to 2.5 hours after administration of 400 mg/kg LP1845 (Figure 2A).[16] A similar pattern was seen with 240 mg/kg hydroxylamine hydrochloride (Figure 2B), although with hydroxylamine, methemoglobin reached maximum levels later than with HAN. The significance of this difference cannot be determined because of the small number of dogs used in this study.

The rise in methemoglobin corresponded with a drop in P_{O2} in dogs treated with all three substances (Figure 3). In addition, LP1845 and HAN, but not hydroxylamine, caused a severe progressive decrease in systemic blood pressure (Figure 4). This response was presumed to be due to

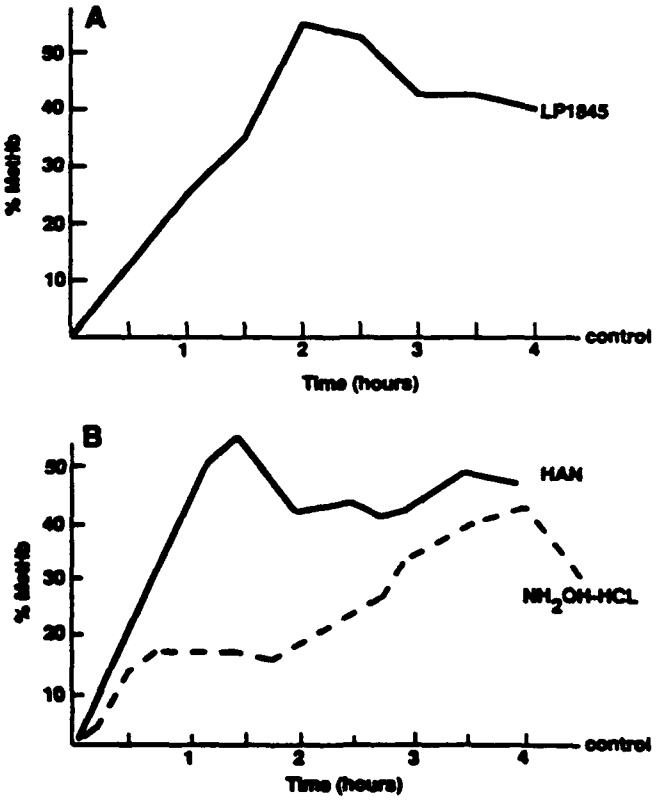

FIGURE 2. Mean methemoglobin values after oral administration of (A) 400 mg/kg LP1845 or (B) 240 mg/kg HAN or 240 mg/kg hydroxylamine to dogs. Data from Metker et al.[12]

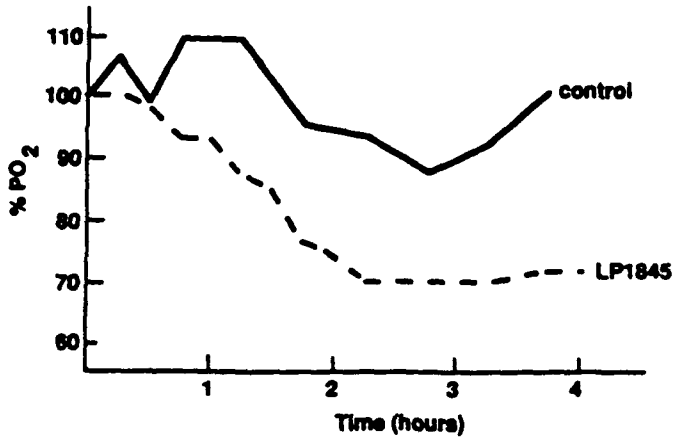

FIGURE 3. Reduction of arterial oxygen tension following oral administration of 400 mg/kg LP1845 to dogs. Data from Metker et al.[12]

peripheral vasodilation resulting from the high nitrate content of these materials.[16] The result for hydroxylamine in Figure 4 are in apparent conflict with a report[17] which showed that bolus intravenous doses of hydroxylamine hydrochloride produced transient, precipitous falls in mean arterial blood pressure.

Oral Exposure: Repeated Dose

HAN was administered by gavage to groups of six male New Zealand White rabbits in doses of 1, 5, and 25 mg/kg/day for 21 consecutive days. The most notable findings at the end of the test period were spleen enlargement and anemia.[11]

Inhalation Exposure

Male and female rats and male beagle dogs were exposed to aerosolized HAN 6 hours/day, 5 days/week for 13 weeks at concentrations of 33, 100, or 300 mg/m^3. Dose-related effects occurred in both species and were characterized in rats by weight loss and spleen and liver enlargement. In dogs, respiratory irritation, blood dyscrasia, and elevated methemoglobin were the major toxic effects. Minimal effects were observed at the lowest dose.[18]

Dermal Exposure

LP is a strong skin irritant. A single, topical application of LP1846 to the skin of Hanford miniature swine causes erythema within several hours. By 24 hours after application, the erythema and edema are severe. Within 24 to 48 hours, there are extensive vesicles and papules. A surface crust begins to form by day 4, and healing is complete within 2 weeks.[3]

The histopathologic effects of repeated application of LP on rabbit skin have been described as "ulcerative dermatitis" with "marked necrosis and loss of epidermis." Histopathologic examination revealed "intense acute and chronic inflammatory infiltrates extending from the base of the epithelial necrosis into the dermis. Often, there was superficial crusting composed of necrotic cellular debris and keratin."[19]

Single- and repeated-dose dermal studies have shown that LP and HAN readily penetrate the skin to produce characteristic systemic effects. In a study in rabbits, HAN and LP were repeatedly applied to the skin for 21 days. The test material was applied in six doses ranging from 0.7 to 11.7 mg/kg, and treated areas were covered with a nonocclusive patch. The higher doses caused erythrocyte destruction, Heinz body formation, anemia, and spleen enlargement. Dermal necrosis was observed at all doses tested.[19]

Recent dermal studies using the Hanford miniature pig were designed to simulate potential human accident scenarios. In the first of these studies, LP1846 was applied to 15% of the body surface,[8] assuming this would be the skin surface contacted if sufficient LP was spilled on a soldier to cover the front surface of the body below the waist. LP was applied directly to the skin of two pigs with the use of a cotton sponge. Two other pigs received the same volume of material on a swatch of battle dress uniform fabric. In the latter case, the skin was lightly rubbed with the swatch for 5 minutes to produce mild abrasion and the swatch was held in place with a porous elastic patch for 24 hours.

All four animals were listless and had pale mucous membranes by 24 hours after treatment. At 24 hours, LP1846

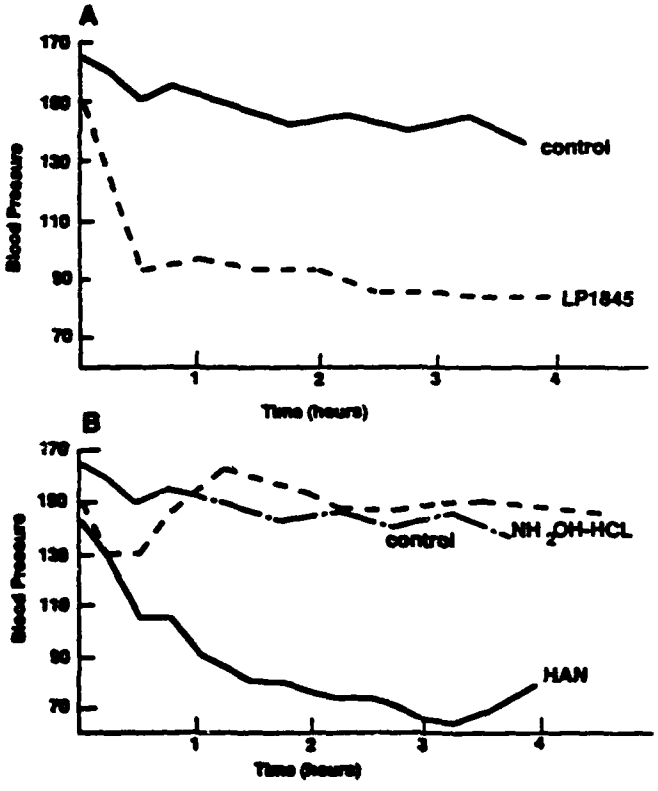

FIGURE 4. Mean blood pressure following oral administration of (A) 400 mg/kg LP1845 or (B) 240 mg/kg HAN or 240 mg/kg hydroxylamine to dogs. Data from Metker et al.[12]

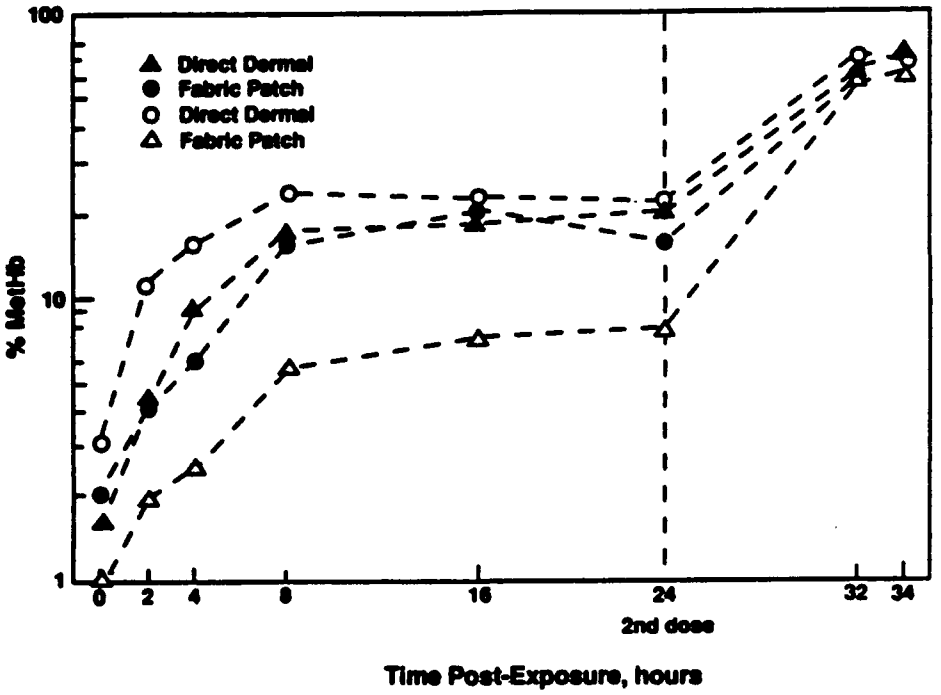

FIGURE 5. Methemoglobin levels in swine treated dermally with two successive doses of LP1846. Data from Weller et al.[8]

was reapplied to the same skin area by the same technique used in the initial treatment. Approximately 8 hours later, all four animals were moribund, markedly cyanotic, tachypneic, and vomiting. Methemoglobin levels reached about 20% after the first treatment and rose to about 65% after the second treatment (Figure 5). Heinz bodies were present in nearly 100% of the erythrocytes within 16 hours after the first exposure.[8]

Further studies with Hanford miniature swine showed that the methemoglobin response is positively related to the applied dose.[3] Figure 6 shows the mean methemoglobin levels in groups of animals that received a range of doses. Animals were treated with undiluted LP1846 on 0%, 1%, 5%, 10%, and 15% of their body surface. Methemoglobin levels were unchanged with 1% LP1846 (the no-effect level) but increased positively with higher doses.

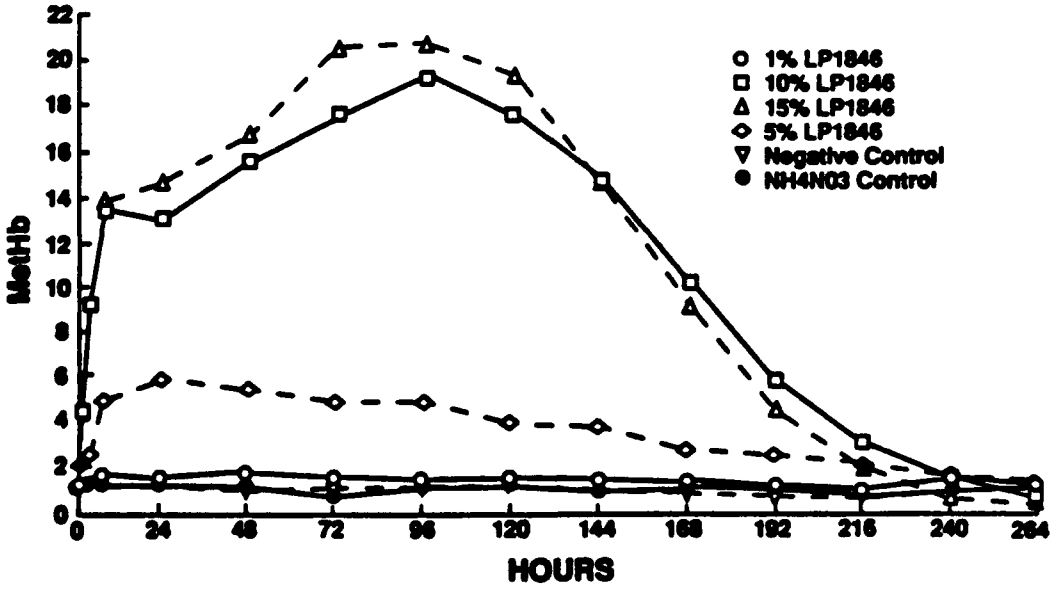

FIGURE 6. Methemoglobin levels in swine treated dermally with single doses of LP1846. Data from Witt et al.[20]

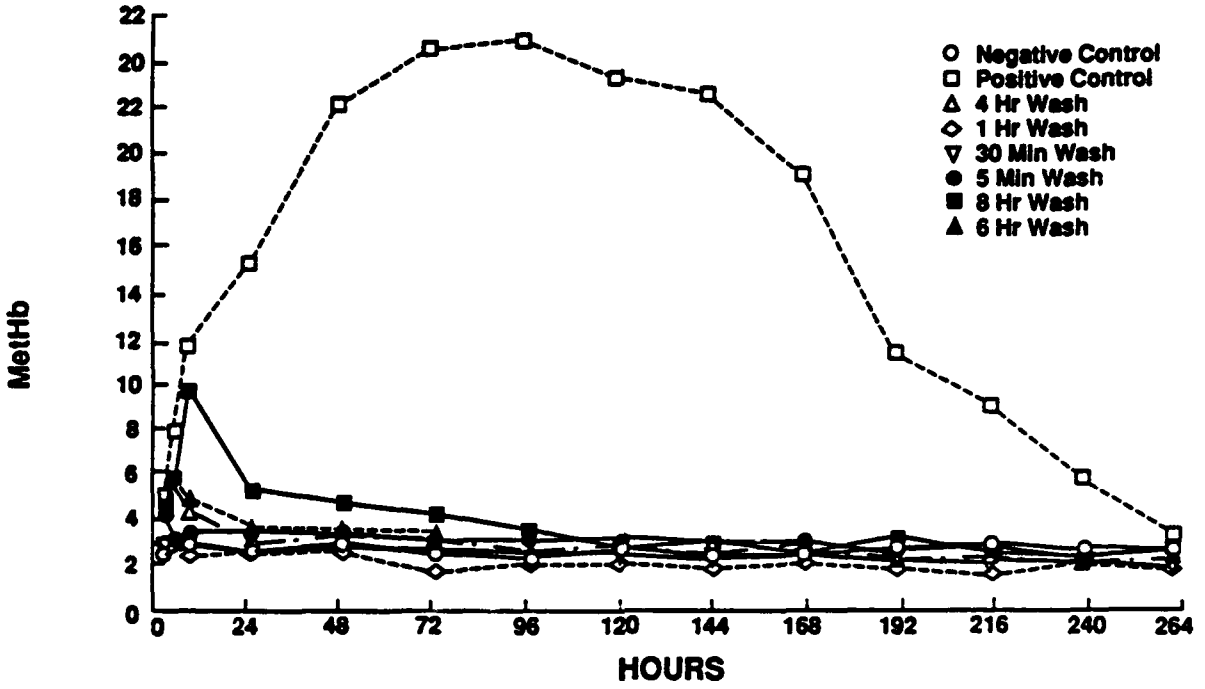

FIGURE 7. Effect of rinsing on methemoglobin levels at various times after topical application of LP1846 to swine. Data from Witt et al.[20]

A recent study[20] clearly demonstrated that rinsing the skin within several hours after exposure effectively reduces the severity of skin lesions and reverses the methemoglobin response. In this work, undiluted LP1846 was applied to 10% of the body surface of Hanford miniature swine. The skin lesions were minimal if treated areas were rinsed within 4 hours after exposure. Some vesicles formed if the skin was rinsed 8 hours after exposure, but the severity of these lesions was much less than those of unwashed controls. The effect of rinsing on methemoglobin levels is shown in Figure 7. Methemoglobin levels began to decline immediately after rinsing if the skin was rinsed at any time up to 8 hours after treatment (longer time periods were not examined). For example, methemoglobin levels were up to about 5.5% before the wash at 8 hours. Although the levels rose steadily to about 13% by day 3 in unwashed controls, they were reduced to 3% by 24 hours and were normal by 4 days after treatment in rinsed animals.

Exposure Assessment

The design of the weapon system has evolved continuously since the beginning of this project, and as a result, the developer is currently working on the third-generation-use scenario. Interactions between the developer and health specialists at USABRDL have led to identification of critical processes/operations where exposure potential could be significant. The weapons system design has been refined to reduce or eliminate these nodes. The use scenario incorporates the entire logistics system (Figure 8). Among the more important safety aspects considered in the use scenario are the types of materials that can be safely used for LP storage and transfer. These materials must be compatible with LP in order to prevent degradation. Degradation products

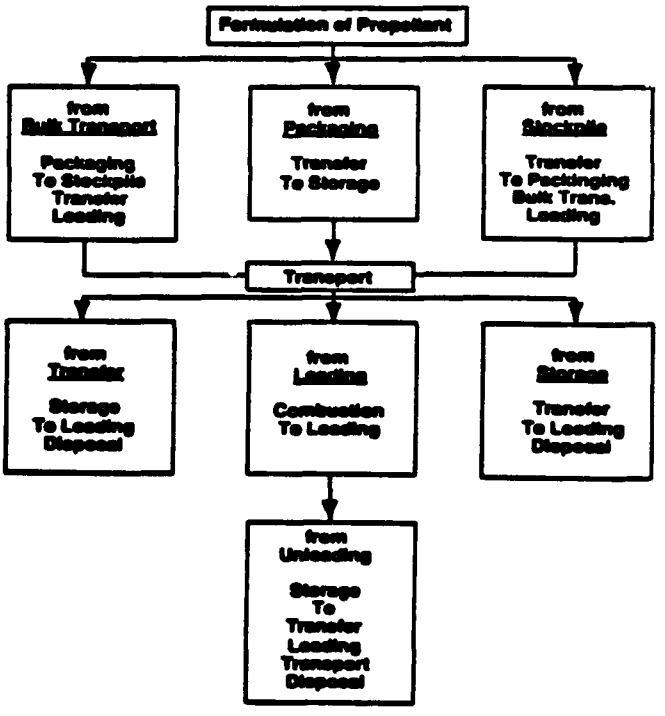

FIGURE 8. Liquid gun propellant cycle. Following formulation, propellant may move between boxes as indicated.

(e.g., nitric acid) may preclude use of LP as a propellant and may also increase the toxicity of the propellant. Mechanisms for liquid transfer have been devised that can reduce the requirement for manual activity. Operations that involve a high potential for liquid spills, such as the gun breech mechanisms, have been automated and isolated from the crew as much as possible.

Data Requirements for Risk Assessment

The basic elements being considered in the risk assessment of LP are shown in Table II. Three of these elements (skin damage, methemoglobin production, and red blood cell destruction) are the major health effects of LP. The remaining elements represent the mechanisms by which exposure produces these health effects. The following simplified dermal exposure formula, taken from the U.S. Environmental Protection Agency (EPA) Superfund Manual,[21] contains most of the critical elements associated with exposure via the dermal route:

$$DEX = t_e \times AV \times C \times PC \times F \times 1\ L/1000\ cm^3 \div BW \div 2.56 \times 10^4\ days/lifetime$$

where: DEX = estimated dermal exposure (mg/kg/day)
t_e = duration of exposure (hrs/event)
AV = skin surface available for contact (cm^2)
C = contaminant concentration in water
PC = dermal permeability constant for the subject contaminant (cm/hr)
F = frequency of exposure events per lifetime
BW = average adult body weight (70 kg)
1 L/1000 cm^3 = volumetric conversion constant for water

In the case of LP, data for two components of this model, duration and frequency of exposure, are being developed by the weapons developer. When the frequency and duration of potential exposures have been addressed, external dose must be estimated. EPA has conducted studies demonstrating that film thickness represents a reasonable upper boundary on the degree of skin exposure that could occur because the excess will run off.[22] Exploration of film thickness properties of LP, adjusted by the affected surface area, may provide a reasonable approach to estimates of external dose resulting from a spill incident.

A number of mechanisms for skin injury and/or dermal penetration have been proposed. Classical dermal penetration models for many substances are based upon affinity with lipid materials in the stratum corneum. Most models of dermal penetration use the octanol/water partition coefficient as an index of lipid solubility. LP, however, cannot depend upon lipid solubility as a route of entry because HAN and TEAN, which are ionized at the pH of the skin surface (pH 5), reside almost exclusively in the aqueous phase.

Other procedures for predicting dermal irritation use the pK_a or acid dissociation constant. Berner et al.[23,24] showed

TABLE II. Outline of Data Requirements for Risk Assessment

- Exposure
- Dermal penetration
  - Mechanisms
  - Pig-to-man extrapolation
- Dermal irritation (end point)
- Methemoglobin production
  - Mechanisms
  - Pig-to-man extrapolation
- Methemoglobin reduction
  - Mechanism
  - Pig-to-man extrapolation
- Methemoglobin level (end point)
- RBC destruction and Heinz body formation (end point)

that a pK_a greater than 8 or less than 4 is highly predictive of acute skin irritation for acids and bases in man. This is of less importance for HAN and TEAN whose pKa values are 5.96 and 7.76, respectively.

A further line of inquiry for the mechanism of skin penetration by LP is to explore the route of entry through direct destruction of the stratum corneum and other superficial layers using nitric acid as a model. (Nitric acid is a common manufacturing contaminant in LP.) Most work published in this area focused on the relationship between the strength of the acid and the degree of necrotic tissue development. There are some data on the association between the size of the lesion and the increase in methemoglobin.

Skin damage may also be caused by hydroxylamine or other breakdown products of HAN, which is unstable at physiological pH. One such product, ammonia, is known to produce skin blisters. Hydroxylamine can cause necrosis, and as described above, its ability to produce methemoglobin correlates with the observed effects of contact with LP.

Current swine dermal studies are examining the morphologic and histologic changes brought about by LP. Destruction of the stratum corneum is probably related to denaturation of protein by reducing and oxidizing ions in the LP mixture such as nitrate. Butler showed that hydroxylamine can cleave the peptide bonds (asparagine-glycine) in collagen.[25]

The studies in swine will serve as the basis for continuing work on the risks associated with exposure to LP. Inherent in this work is the assumption that swine can serve as an appropriate model for LP skin penetration and methemoglobin production in humans. There are sufficient data in the literature to support use of swine as a model for the production and reduction of human methemoglobin. A few examples are offered for illustration (Table III). In 1965, Rivkin and Simon[26] incubated nitrite-treated red blood cells with various substrates. The methemoglobin reduction rates were similar between human and pig cells in lactate and plasma. The enzyme responsible for reduction of methemoglobin in mammalian erythrocytes is nicotinamide adenine dinucleo-

TABLE III. Metabolism of Pig Erythrocytes Methemoglobin Reduction in Intact Red Cells

	Human	± 2 S.D. μM/g Hemoglobin/hr[A]		Pig	± 2 S.D.[A]	
Substrates						
Plasma	1.3	(2)		1.6	0.84 (8)	
Glucose	1.1	0.46 (8)		0.5	(4)	
Lactate[B]	1.3	(1)		2.0	(2)	
Lactate	1.1	(1)		1.1	0.50 (5)	
Inosine	1.3	0.46 (8)		1.6	(2)	
Ribose	—	—		0.7	(1)	
Buffer	0.2	(1)		0.34	(4)	
Substrates with methylene blue (MB)			R[C]			R[C]
Plasma				2.0	(3)	1.2
Glucose	13.2	2.2 (8)	12	0.8	(2)	1.6
Lactate				1.3	(1)	1.2
Inosine	15.3	3.7 (8)	12	6.3	(2)	4.0
Ribose				0.95	(1)	1.4
Buffer				0.5	(1)	1.5
Plasma + inosine				6.6	(1)	3.3

[A]Number of specimens tested appears in parentheses.
[B]Lactate concentration 20 μM/ml; all other substrate concentrations 10 μM/ml.
[C]R = with MB ÷ without MB.
Source: Rivkin and Simon.[28]

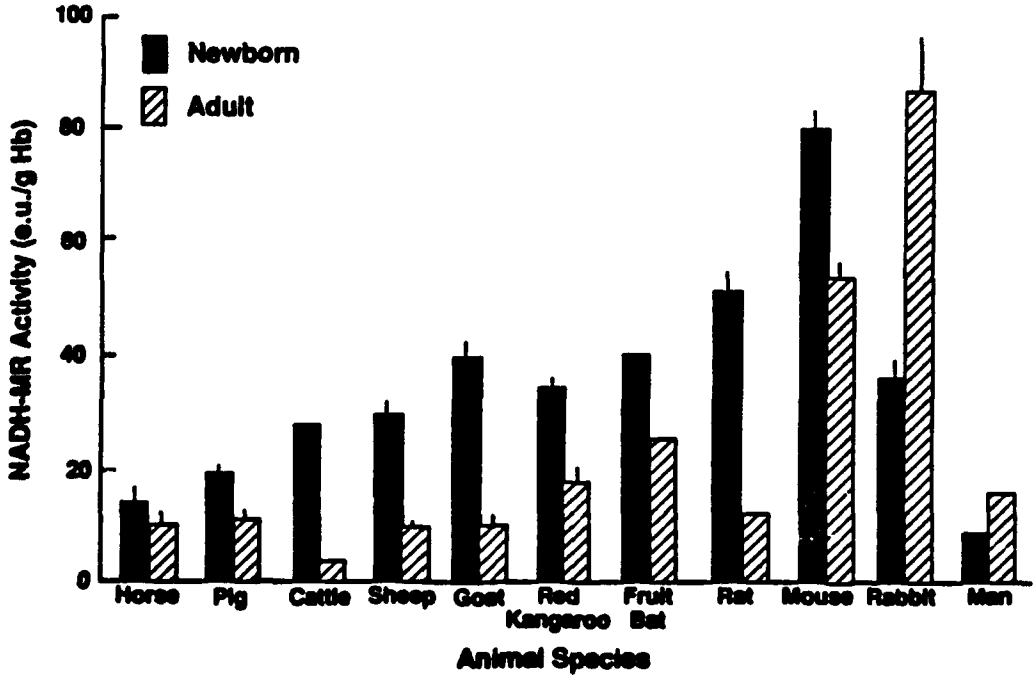

FIGURE 9. Activity of NADH-Methemoglobin Reductase in the erythrocytes of newborn and adult mammals (x ± SEM). Data from Lo and Agar.[27]

tide-linked methemoglobin reductase. In Figure 9, the reductase activities of several species were measured in hemolysate; pig and human activity were comparable.[27] In Table IV, activities of two different forms of reductase found in both pig and human were compared and found to be equivalent.[28] These illustrations indicate that close parallels can be established between the kinetics of methemoglobin formation and reduction in pig and man. The data from the literature will be compared with methemoglobin formation and reduction in the LP studies to establish appropriate coefficients.

The final step in the assessment of risk will be to determine standards appropriate to the observed end points and to evaluate the desirability of developing field-expedient first aid measures for accidental exposures. Dermal irritation and lesion formation should be classified by a military clinical physician or dermatologist in terms of levels of injury requiring self-treatment, treatment by a field medic, or evacuation for hospitalization. The value of methemoglobin as an end point for assessing toxic effects in exposed humans will also be examined. There appears to be some confusion in the literature about the debilitating effects of methemoglobin; older reports draw parallels with carboxyhemoglobin. Unlike carbon monoxide-induced carboxyhemoglobin, hydroxylamine has been reported to not only produce methemoglobin but also sulfhemoglobin and vasodilation.[2,17] There is no definitive agreement on the significance of Heinz body formation for exposures of short duration.

Summary

An approach to the development of data to support a risk assessment on a specific military application of LP has been described. The derivation of data for each of the categories described includes uncertainty associated with each of the variables. What is unique to this exercise is that health risk is being assessed for a system still in the planning stages, and it will play a major role in determining whether to progress with the use of the LP concept.

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TABLE IV. Nicotinamide Adenine Dinucleotide-Linked Methemoglobin Reductase (NADH-MR) and Nicotinamide Adenine Dinucleotide Phosphate-Linked Methemoglobin Reductase (NADPH-MR) Activities in the Erythrocytes of Various Mammalian Species

		NADH-MR[A]		NADPH-MR[A]	
Species		No. of Cases	Mean ± S.E.M.[B]	No. of Cases	Mean ± S.E.M.
Human	Adult	64	2.50 ± 0.06	14	0.15 ± 0.01
	Newborn	26	1.59 ± 0.07	22	0.13 ± 0.04
Cattle	Adult	17	1.74 ± 0.07	14	0.11 ± 0.01
	Newborn	7	5.71 ± 0.26	7	0.29 ± 0.04
Sheep	Adult	10	2.25 ± 0.17	7	0.08 ± 0.01
Horse	Adult	6	2.30 ± 0.14	6	0.17 ± 0.02
Dog	Adult	3	2.63 ± 0.10	3	0.11 ± 0.01
Pig	Adult	11	2.50 ± 0.19	6	0.03 ± 0.01
	Newborn	6	2.17 ± 0.28	6	0.08 ± 0.01
Rabbit	Adult	10	6.80 ± 0.16	6	0.28 ± 0.01
	Newborn	2	6.25 ± 0.13	2	0.30 ± 0.09
Guinea pig	Adult	6	4.95 ± 0.20	6	0.29 ± 0.04
	Newborn	6	4.89 ± 0.24	6	1.11 ± 0.12
Rat	Adult	14	2.46 ± 0.04	8	0.13 ± 0.01

[A]The results are expressed as units of methemoglobin reductase; 1 unit is equivalent to 1 nmole of methemoglobin reduced/minute/mg hemoglobin.
[B]S.E.M. = Standard Error of the Mean.
Source: Agar and Harley.[28]

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Site-Specific Environmental Assessment

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The following is the abstract of the presentation by Mr. Gardner and Mr. Stachiw. Their paper was not available for publication at this time.

Remediation of historical contamination of the environment at various Department of Defense sites is requiring the expenditure of increasing resources. Many of these sites are contaminated with very complex mixtures of chemicals representing a variety of chemical classes. These chemicals and their degradation by-products often present a formidable hazard identification problem that seriously challenges the principles of the classical risk-based calculation approach. The U.S. Army Biomedical Research and Development Laboratory (USABRDL) has been developing an Integrated Biological Assessment means for assessing the hazards posed by such sites.

Integrated Biological Assessment is the result of carefully selected *in vivo* toxicity assays, *in vitro* assays, and chemical analyses of specific surface or ground waters conducted on-site in a mobile laboratory. To assess the potential chronic hazard posed by a ground, effluent or surface water, a new bioassay using two species of small fish has been developed. These vertebrate animals share many anatomical, biochemical, and genetic characteristics with mammalian animals. The animals are exposed to a variety of concentrations of the test water and are then sacrificed and examined for evidence of histopathological anomalies. The opportunity to perform an on-site, chronic bioassay on the complex mixture of interest employing several thousand vertebrate, nonmammalian animals remains a compelling advantage of this new bioassay.

Developmental toxicity of test waters is assessed using an amphibian embryo assay. The Frog Embryo Teratogenicity Assay Xenopus (FETAX) has been refined with USABRDL support. This method allows one to determine the developmental hazard of test waters by exposing frog embryos to varying concentrations of the material of concern. The FETAX assay allows both the determination of potential human hazard as well as the assessment of ecological (amphibian) impact with the same data set.

Mutagenicity assays, acute aquatic organism toxicity tests, and routine chemical analysis are also simultaneously conducted on the water of interest, affording a powerful integrated assessment of hazard. This measure can be used to prioritize sites for remediation; compare pretreatment water with posttreatment water, yielding insights into remediation efficacy; and provide long-term monitoring data for tracking trends in the potential hazards associated with contaminated environmental sites.

Initial applications of the Integrated Biological Assessment approach are being pursued at Aberdeen Proving Ground, Maryland. This site affords a number of opportunities to conduct this research in an extremely challenging operational scenario.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Research was conducted in compliance with the Animal Welfare Act, and other Federal statues and regulations relating to animals and experiments involving animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, NIH publication 86-23, 1985 edition.

New Directions in Chemical Risk Assessment Methodologies

Biologically Based Models in Risk Assessment

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Dose–response characterization in the risk assessment process for chemical carcinogens entails extrapolation of tissue dosimetry and tumor response seen at high exposure concentrations in test animals to humans exposed to much lower concentrations. The difficulty in predicting the potential human tumor incidence arises from interspecies differences in tissue susceptibility and from the dose, species, and/or exposure-route dependency of chemical disposition. These extrapolations are usually conducted with "mandated" models, a linearized, multistage, cancer model for low-dose extrapolation and a body surface or body weight correction for interspecies extrapolation. In recent years, there have been several attempts to provide an increasing level of biological realism to these extrapolation models. Biologically based dosimetry and response modeling approaches enable identification and characterization of critical determinants of chemical disposition and tissue response and form a mechanistic basis for dose, species, and exposure-route extrapolations. This paper briefly outlines the utility of biologically based models in predicting tissue dosimetry and response and provides an example of the use of biologically based dosimetry models in cancer risk assessment for methylene chloride.

Introduction

Risk assessment is the process of determining the probability and magnitude of adverse health effects associated with human exposure to chemicals. The process of risk assessment is conducted in four parts: hazard identification, exposure assessment, dose–response assessment, and risk characterization.[1] Once a substance is identified as hazardous, the health risks associated with human exposure to that chemical are characterized by combining quantitative information on its exposure levels and dose–response relationship. The dose–response assessment provides the critical piece of information; namely, the nature and extent of adverse health effects associated with chemical exposure. This process includes the extrapolation of response incidence rates observed at high doses to those expected at low doses in test animals and the extrapolation of toxicologically equivalent dose from test animals to humans.

In conventional cancer risk assessment, the high-to-low-dose extrapolation is performed using a linearized, multistage model, and interspecies extrapolation is conducted using a conversion factor based on body weight (BW), usually $BW^{2/3}$ or BW^{1}.[2] The former is considered as scaling on the basis of body surface, whereas the latter is direct body-weight scaling. In general, these "mandated" extrapolation approaches are used regardless of knowledge of the mechanisms of disposition and toxicity of chemicals. The uncertainties associated with the conventional dose–response assessment can be reduced with a mechanistic understanding of the disposition and action of chemicals. This can effectively be performed with the development of biologically based models for tissue dosimetry and tissue response.

Biologically Based Dosimetry Models

Biologically based, tissue dosimetry modeling involves the development of integrated mathematical descriptions of the complex interplay of physiological and chemical-specific factors involved in the uptake and disposition of chemicals. In this approach, the body is divided into a number of tissue compartments, characterized with appropriate blood flow and solubility characteristics (Figure 1). When blood flow is rate-limiting for tissue uptake, tissues are described as homogeneous, well-mixed compartments. If, however, diffusion is rate-limiting, both tissue blood and cellular matrix are described separately. The rate of change in the amount of chemical in these subcompartments is described by a set of mass balance differential equations of the following form:

For tissue,

Rate of change in the amount of chemical in tissue matrix =
Net tissue flux from blood
+ Rate of formation
– Rate of metabolism
– Rate of clearance (1)

For blood in tissue,

Rate of change in the amount of chemical in blood =
Net flux from tissue
+ Net retention from blood flow (2)

If the diffusion from blood to tissue is slow with respect to total tissue blood flow, both equations are necessary. If blood flow is slow with respect to diffusion, these two equations reduce to a single equation to describe the rate of change in amount of chemical in whole tissue mass.

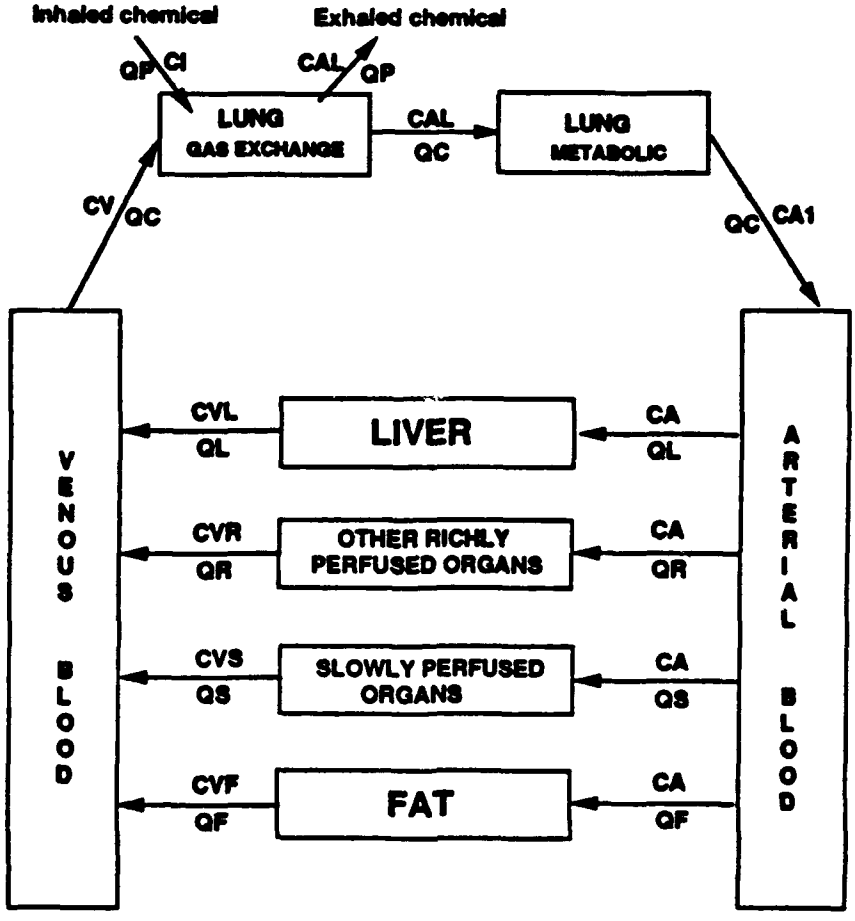

FIGURE 1. Structure of a biologically based dosimetry model. Q terms are air and blood flow rates. C terms are concentrations. These are followed by letters A, AL, A1, F, L, R, S, or V, which represent arterial blood, blood leaving the gas-exchange lung compartment, blood leaving the metabolic lung compartment, fat, liver, richly perfused tissues, slowly perfused tissues, and venous blood. QC, QP, and CI are cardiac output, alveolar ventilation rate, and the concentration of the chemical in the inhaled air.

Rate of change in the amount of chemical in tissue =
Qt(Ca – Cvt) + Rate of formation
– Rate of metabolism
– Rate of clearance (3)

where: Qt = rate of blood flow to tissue "t" (L/hr)

Ca = concentration of chemical in arterial blood (mg/L)

Cvt = concentration of chemical in the venous blood leaving the tissue (mg/L)

Then, the effluent venous blood concentration is in equilibrium with the total tissue concentration (Ct) as specified by the tissue:blood partition coefficient (Pt), such that Cvt = Ct/Pt. Rate of formation in these equations represents the rate of appearance of a chemical in the tissue through biotransformation of a precursor. The metabolism term represents loss of the substance because of chemical reactions. Clearance, as specified in these equations, corresponds to the loss of the intact chemical from the tissue. Examples include biliary or urinary excretion.

The effluent blood from all organs mixes in the venous blood compartment yielding a mixed venous blood concentration (Cv). With a volatile chemical, an algebraic relationship can be used to describe the equilibration of chemical between arterial blood and alveolar air.[3] The arterial blood in this model then flows through a metabolic

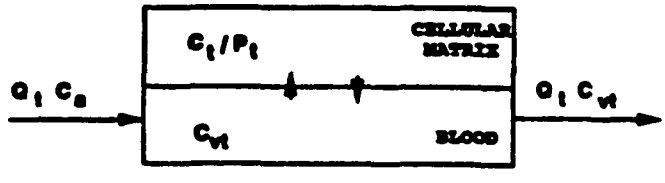

FIGURE 2. Schematic of a tissue compartment. Qt is tissue blood flow rate, Ca is the arterial blood concentration of the chemical, Cvt is the concentration of the chemical in the venous blood leaving the tissue, Ct is the tissue concentration, and Pt is the tissue:blood partition coefficient of the chemical.

lung compartment, if appropriate, as in the case of methylene chloride.[3] Finally, the chemical leaves this lung tissue compartment via the systemic arterial blood with concentration Ca and is delivered to all other organs (Figure 2).

This type of biologically based dosimetry model has been developed for a number of individual chemicals and also for binary mixtures of chemicals with toxicological properties.[4] The principal application of the biologically based dosimetry models is to predict target tissue dose of the toxic parent chemical or its reactive metabolite. Using the internal dose of the toxic moiety of a chemical in risk assessment calculations provides a better basis of relating to the observed toxic effects than does the external or exposure concentration of the parent chemical. Because biologically based dosimetry models facilitate the prediction of target tissue dose in people, they can help reduce the uncertainty associated with the conventional extrapolation procedures. Such an application has been demonstrated with dichloromethane,[3] which is discussed below.

Biologically Based Dosimetry Models in Risk Assessment: An Example

Dichloromethane (CH_2Cl_2; methylene chloride; DCM), caused liver and lung tumors in mice exposed at 2000 or 4000 ppm, 6 hours/day for their lifetime.[5] DCM is metabolized by two processes: 1) oxidation, leading to the production of highly-reactive formyl chloride, as well as carbon monoxide and small amounts of carbon dioxide and 2) glutathione (GSH) conjugation, yielding chloromethyl glutathione, another reactive intermediate, and carbon dioxide as an end product.[6,7] Either of the reactive metabolites resulting from oxidation or GSH conjugation could be involved in the mutagenic changes leading to cancer. In the biologically based dosimetry model for DCM, these metabolic pathways were described according to their different kinetic characteristics. DCM metabolism in lung and liver was described with a saturable term for oxidation (Vmax, Km) and a linear term (Kf) for reaction with GSH.[3,8] Thus,

$$\text{Rate of DCM metabolism} = \frac{\text{Vmax} \times \text{Cvt}}{(\text{Km} + \text{Cvt})} + \text{Kf} \times \text{Cvt} \times \text{Vt} \qquad (4)$$

where: Vmax = maximum enzymatic reaction rate for oxidation (mg/hr)
Km = Michaelis constant for oxidation (mg/L)
Kf = first-order rate constant for glutathione conjugation (per hour)
Vt = volume of the tissue (L)

At low exposure concentrations (Km > > Cvt), the effective rate constant for oxidation (Vmax/Km) is nearly 100-fold higher than that for GSH conjugation (Kf). The biologically based dosimetry model predicts that the tissue exposure to metabolites derived from both these pathways would be nonlinear in the exposure range of 0 to 4000 ppm DCM.[3] Oxidation quickly saturates, so its contribution is essentially unchanged from 2000 to 4000 ppm. With the GSH pathway, there is little contribution until the oxidative pathway saturates at about 300 ppm, then its contribution increases linearly with increasing exposure concentration (Figure 3). Tissue exposure to DCM itself also increases linearly with dose between 2000 and 4000 ppm.

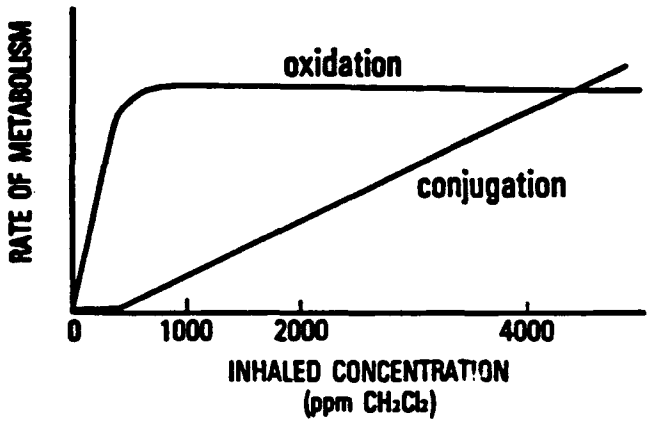

FIGURE 3. Schematic representation of the model predictions of the rate of metabolism of dichloromethane via glutathione conjugation and oxidative pathways at various exposure concentrations.

When tumor incidence was compared to the calculated tissue exposure to metabolites derived from these two pathways (as the amount of DCM metabolized by the pathway/organ volume/day), there was a correlation of tumor incidence with the GSH conjugation metabolites but not with the oxidative pathway metabolites (Table I). Furthermore, the GSH pathway, and not the oxidative pathway, had been associated with mutagenesis in bacteria,[9] and more recently, formaldehyde formed from the GSH pathway has been shown to react with DNA at least in the liver of the mouse.[10] Based on the available body of evidence, the metabolite(s) arising from the GSH pathway were believed to be related to DCM carcinogenesis. The subsequent risk assessment for DCM was then conducted on the basis of the estimates of the tissue dose of DCM–GSH conjugate predicted using the biologically based dosimetry model.[3]

The target tissue dose of the metabolite arising from the GSH pathway at low doses of DCM was calculated using the biological dosimetry model, and its relationship to tumor response was examined using a linearized, multistage model. The high dose to low dose extrapolation of tissue concentrations of DCM–GSH metabolite was highly nonlinear because oxidation, not GSH conjugation, is favored at low DCM exposure concentrations. Interspecies extrapolation was also carried out based on a presumption that a similar, daily, tissue dose of DCM–GSH metabolite would give rise to a similar tumor outcome regardless of the species. This biologically based approach leads to a prediction that the human tissue

TABLE I. Tumor Incidence and Calculated Tissue Dose of Dichloromethane (DCM) and Its Metabolites Following Inhalation Exposures of 0, 2000, or 4000 ppm DCM in Female Mice

DCM Exposure Concentration	Tumor Incidence (%)	Tissue Dose (Amount in mg/L Tissue/Day) GSH Pathway	Oxidative Pathway	DCM
		A. LIVER		
0	6	—	—	—
2000	33	851	3575	362
4000	83	1800	3701	771
		B. LUNG		
0	6	—	—	—
2000	63	123	1531	381
4000	85	256	1583	794

dose of DCM–GSH conjugate would be significantly less than that of the mouse at equivalent exposure concentrations. This conclusion contrasts to that obtained by the U.S. Environmental Protection Agency (EPA) which estimates that people are more sensitive than mice based on the use of a body surface area scaling factor.[11]

In the DCM risk assessment conducted with the target tissue dose estimated using the biologically based dosimetry model, the predicted human low-dose cancer risk was about 100- to 200-fold less than that predicted by EPA using the standard default assumptions.[3] Since 1987, several refinements of the risk estimates have appeared based on improved measures of DCM metabolism in test animals and people.[8] The differences between the default and physiologically based pharmacokinetic (PBPK)-based risk assessment though are still of the same range, about two orders of magnitude even when the new enzyme activity data are considered.[8,11,12]

Even though the biologically based dosimetry modeling approach provided the link between external exposure concentration of DCM and target tissue exposure to its potentially reactive metabolite, the low-dose extrapolation of the relationship between tissue dose of the metabolite(s) and tumor response was still conducted using the linearized, multistage model. An improved strategy would be to develop biologically based response models to provide the link between PBPK-based estimates of tissue dosimetry and response.[13]

Biologically Based Response Models

Biologically based response modeling involves the development of mathematical descriptions integrating the critical elements of the series of events leading to the induction of tissue response. An example of this approach is the Moolgavkar–Venzon–Knudson (MVK), two-stage, cancer model.[14] This model describes carcinogenesis as the end result of two critical events that correspond to mutations. Accordingly, the normal cells first progress to an intermediate cell type after a single mutation. The intermediate cell population may have different growth characteristics from the normal cells but is not malignant. The second mutational event produces cells of a malignant genotype that lead to neoplastic transformation (Figure 4).

The use of this biologically based cancer response model in risk assessment requires quantitative information on the critical parameters involved in the process; namely, the birth and death rates of cells and the mutation rates associated with the production of intermediary and malignant cell population. Because the parameters of the MVK model are interpretable in biological terms, it is possible to examine the carcinogenic potency of chemicals that alter one or more of these parameters. For example, certain chemicals act as genotoxic agents increasing the mutation rates ($\mu 1$, $\mu 2$); others, such as the cytotoxicants, alter cell death and birth rates ($\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$); and, yet, others (e.g., promoters) convey growth advantages to the intermediate cell population ($\alpha 2$, $\beta 2$). Because chemicals often act by more than one mechanism, each of which may be dose–dependent, the incorporation of quantitative information on the critical determinants within a biological modeling framework enables the extrapolation of the relative role of the various mechanisms for different exposure scenarios.

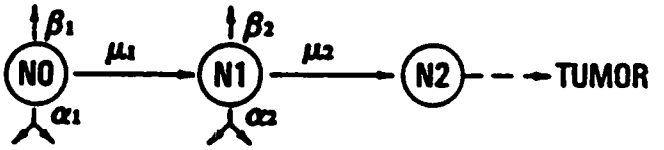

FIGURE 4. Schematic of the two-stage, Moolgavkar–Venzon–Knudson cancer model. N0, N1, and N2 are normal cells, intermediate cells with a single mutation and the cancer cell resulting from two mutational events, respectively; μ represents mutational frequency; α represents cell birth rates and β denotes cell death rates of normal (1) and intermediate (2) cells.

Discussion

A prerequisite for extrapolation of the pharmacokinetic and pharmacodynamic behavior of chemicals is the identification and characterization of the critical determinants of these processes in the test species. The integration of these determinants within a biological modeling framework enables the exposure-route, high-dose-to-low-dose, and interspecies extrapolations of the disposition and action of chemicals.

In biologically based dosimetry modeling, the specified compartments are biologically relevant, arranged in an anatomically accurate manner, and defined with appropriate physiological characteristics. The compartments may represent a single tissue or a group consisting of several tissues with similar blood flow and solubility characteristics (e.g., adrenals, kidney, thyroid, brain, heart, and hepato-portal system are usually pooled into one compartment and are referred to as richly perfused tissues). Even these models represent some level of simplification of the true complexities of biological systems.[15]

The use of a biologically based, dosimetry modeling approach for interspecies scaling of pharmacokinetic behavior of chemicals involves several steps. First, an animal model is developed to describe the uptake and disposition of the chemical. The physiological parameters in the animal model are then scaled, and the chemical-specific parameters are determined for the species of interest (e.g., humans). The model description remains the same, the animal model serving to identify the critical biological determinants of the kinetic processes. Because of the biological reality of the model description, these dosimetry models can be used to examine interindividual differences in chemical disposition, interspecies differences in metabolism, and postexposure metabolism of lipophilic chemicals. These processes cannot be adequately accomodated or described with the use of the conventional allometric scaling approach.[16]

The principal application of the biologically based dosimetry models is in the prediction of tissue exposure to the toxic moiety (e.g., parent chemical, reactive metabolite, macromolecular adducts) regardless of the dose, exposure route, and species. In the DCM example presented in this paper, the low-dose extrapolation of the tissue response was conducted with the linearized, multistage (LMS), modeling approach. The improvement over the conventional methodology is that, here, the independent variable specified in the LMS model, "dose," is not administered dose or inhaled concentration; it is the tissue dose estimated with the biologically based dosimetry model (Figure 5; Path 2a) and defined with some perceived mechanism of action of the carcinogen. The uncertainty associated with the low-dose extrapolation using the LMS procedure can be addressed with the use of biologically

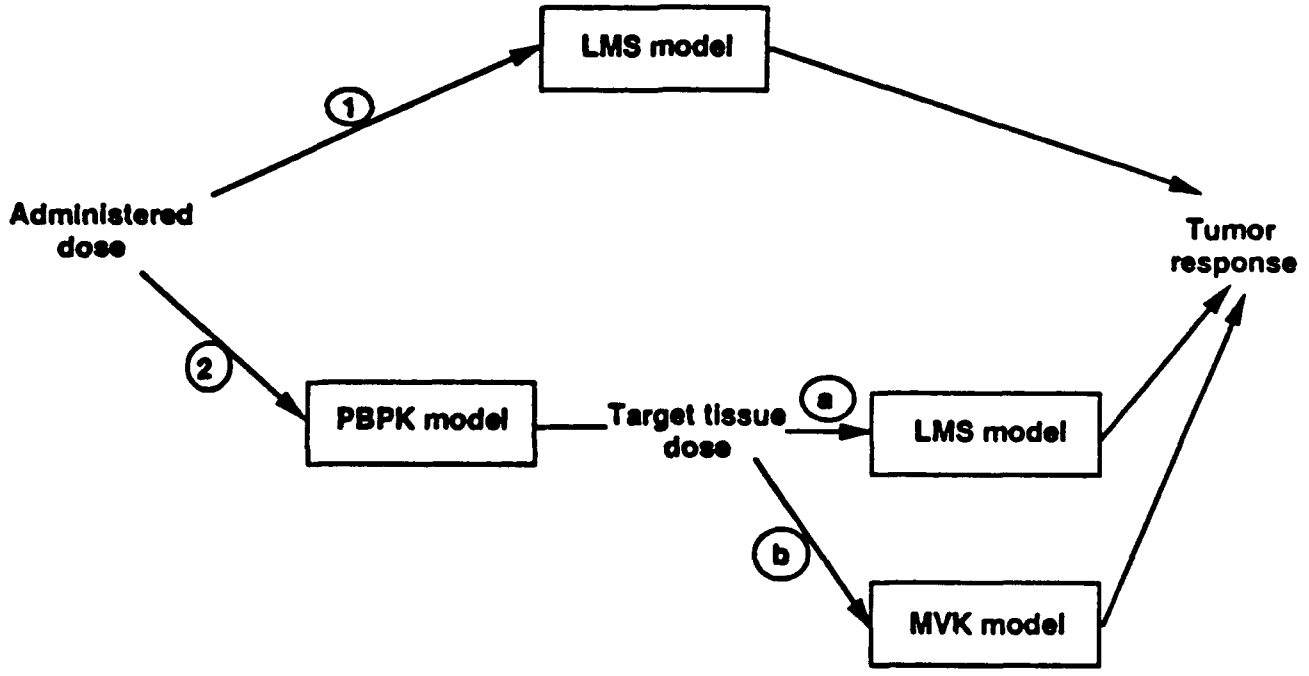

FIGURE 5. Utilization of the various approaches in the low-dose extrapolation of chemically induced tumorigenesis. (1) The conventional approach involves relating the external exposure concentration to the tumor incidence levels using a linearized, multistage (LMS) model. (2a) The physiologically based, pharmacokinetic (PBPK) model-based approach involves the use of this dosimetry model to predict target tissue dose but still uses the LMS procedure to relate to the tumor incidence levels. (2b) An improved strategy would be to develop integrated biologically based dosimetry (PBPK) and response (e.g., Moolgavkar–Venzon–Knudson cancer model) models.

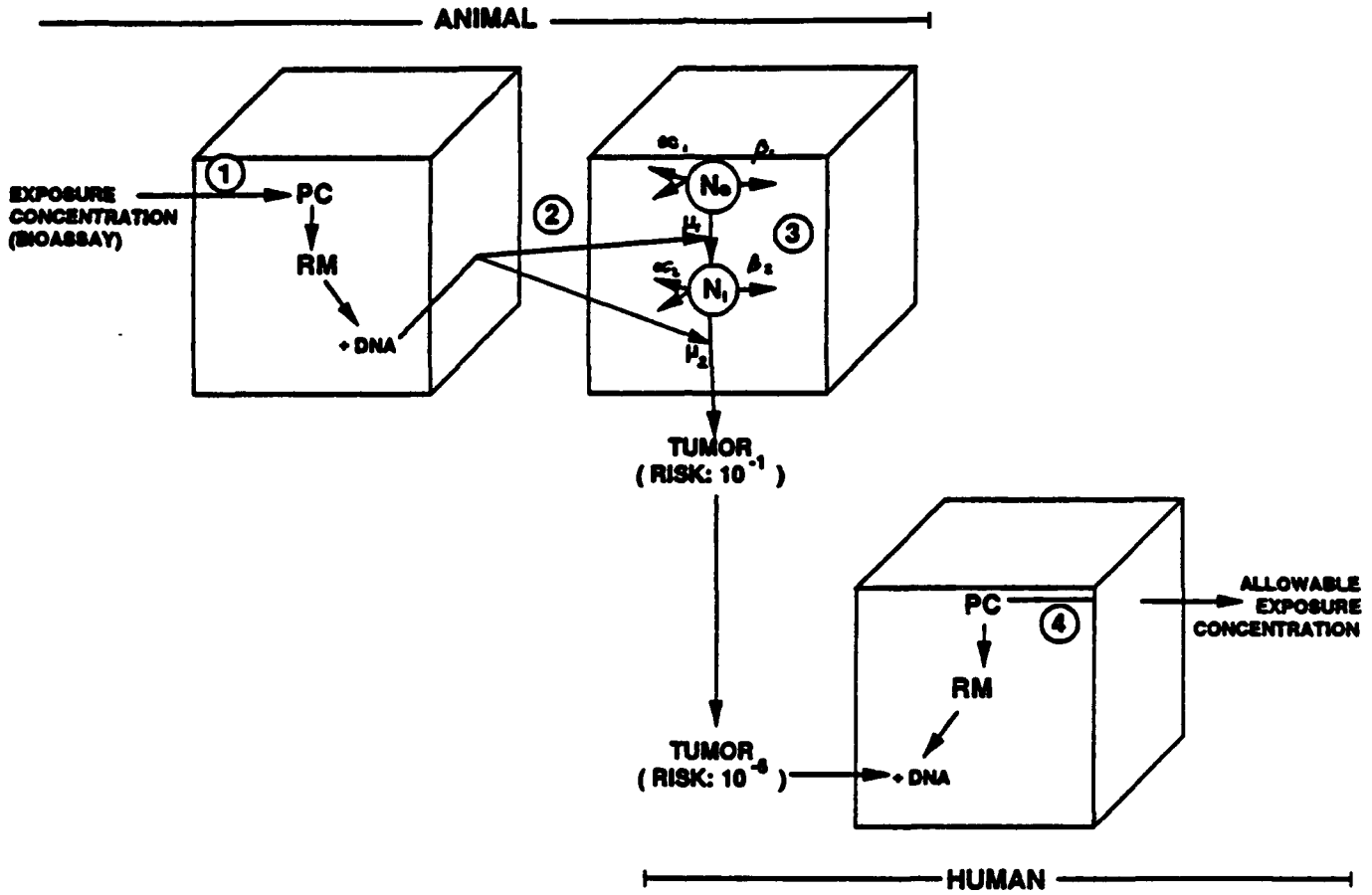

FIGURE 6. Schematic of a biologically and mechanistically based approach for cancer risk assessment. This figure illustrates the strategy for conducting risk assessment for a chemical that acts by a DNA-reactive mechanism to cause cancer. This approach consists of the development of (1) an animal dosimetry model, (2) a quantitative definition of the mechanism of action, (3) an animal tumor response model, and (4) a human dosimetry model. (PC: parent chemical, RM: reactive metabolite, N0: normal cells, N1: intermediate cells, μ1 and μ2: mutation rates, α1 and α2: cell birth rates, β1 and β2: cell death rates).

based response models. The dose–response relationship used in the LMS procedure is not derived from any contemporary biological theory of cancer induction but is a consequence of curve fitting to fit the tumor data to the multistage polynomial. Further, the use of LMS procedure in risk assessment does not permit incorporation of important experimental observations other than tumor incidence data (e.g., cell proliferation). In contrast, the parameters in the MVK model, as in the dosimetry models, are interpretable in biological terms, and therefore, relevant information obtained from experiments supplementary to the chronic animal bioassays can be incorporated into the risk assessment process.[17]

The linkage of the biologically based dosimetry and response models with a quantitative definition of the mechanism of action would further enable the extrapolation of both chemical disposition and tissue response at various doses, exposure routes, and species (Figure 5, Path 2b; Figure 6). In this approach, the animal models serve to identify and characterize the critical biological determinants of disposition, mechanism of action, and tissue response. Whereas, the animal dosimetry model enables the identification of the appropriate dose surrogate for target tissue exposure, the response model provides the quantitative linkage between the series of events leading to the development of a tissue response.[18,19] Further, target tissue exposure to the toxic moiety predicted by the animal dosimetry model can be related to the response model by a quantitative definition of the mechanism of action (e.g., DNA reactivity). Finally, the allowable exposure concentration of a chemical that corresponds to the target tissue dose of the toxic moiety associated with a projected excess incidence of tumors (e.g., one in a million) is determined with the human dosimetry model.

Biologically based models can be used as tools for hypothesis testing. For example, the dosimetry models can be used to test the utility and appropriateness of the conventional extrapolation procedures used for a particular chemical. Thus, allowable exposure concentrations for humans derived with the biologically based dosimetry approach can be compared to those obtained using the body surface correction and LMS procedure. For certain direct-acting chemicals, which are detoxified by enzyme-mediated metabolic processes, it

may be that the conventional approach is satisfactory, whereas in other cases where a saturable metabolic process yields the toxic moiety, the conventional methods might overpredict the health risks associated with human exposure. Similarly, the adequacy of the quantitative description of the mechanism of action can be tested with experimental data on tissue response. When the model fails to predict the observed data, it indicates an incomplete understanding of the processes and the biological determinants involved. The adequacy of a model description depends on the purpose for which it is intended and the depth of understanding of the critical components of the process. Unlike the "mandated" mathematical models used in conventional risk assessment, the biologically based models are versatile and often, but not always, difficult to validate. In contrast to the "mandated" models, which are useful only for generating a risk number, the biologically based models allow integration of various observations, identification of critical data gaps, and estimation of risk numbers, along with attendant appreciation of areas of significant biological uncertainty.

Summary

The biologically based modeling approach leads to the identification, characterization, and integration of the critical biological determinants of chemical disposition and tissue response. The development of such mechanistically and biologically based dosimetry–response models should enhance our ability to confidently predict the risk associated with human exposure to chemicals that cause cancer or various other types of toxicity.

Acknowledgment

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Physiologically Based Pharmacokinetic Modeling and Risk Assessment: The Case of Trichloroethylene

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The following is the abstract of the presentation by Mr. Allen. His paper was not available for publication at this time.

Physiologically based pharmacokinetic (PBPK) models have been developed for describing the behavior of trichloroethylene (TCE) and its important metabolite, trichloroacetic acid (TCA), in rats, mice, and humans. Salient features of the models include the saturable metabolism of TCE, the representation of TCA production as a proportion of that metabolism, and the representation of TCA kinetics with a single volume of distribution that is apparently nonlinearly related to body weight in humans.

TCA has been shown to be carcinogenic when administered to rodents and it is assumed that the carcinogenicity of TCE is, at least in part, due to production of TCA. Several dose surrogates based on TCE metabolism and TCA production were considered for use in cancer dose–response modeling. The values of those dose surrogates have been predicted by the PBPK models for exposure levels used in carcinogenicity bioassays and for exposures of concern for humans. The use of the PBPK model predictions have been used in conjunction with an uncertainty analysis and the impacts on TCE risk estimates have been investigated.

Further information on this subject can be found in AAMRL-TR-90-72, Volume II, "Development and Validation of Methods for Applying PK Data in Risk Assessment: Trichloroethylene," which is available from the National Technical Information Service (AD No. A237366).

Cancer Risk Assessment with Intermittent Exposure

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Applications of methods for carcinogenic risk assessment often focus on estimating lifetime cancer risk. With intermittent or time-dependent exposures, lifetime risk is often approximated on the basis of a lifetime average daily dose (LADD). In this article, we show that there exists a lifetime equivalent constant dose (LECD) which leads to the same lifetime risk as the actual time-dependent exposure pattern. The ratio C = LECD/LADD then provides a measure of accuracy of risk estimates based on the LADD and a basis for correcting such estimates.

Theoretical results derived under the classical multistage model and the two-stage birth–death–mutation model suggest that the maximum value of C, which represents the factor by which the LADD may lead to underestimates of risk, will often lie in the range of two to fivefold. The practical application of these results is illustrated in the case of astronauts subjected to relatively short-term exposure to volatile organics in a closed space station environment and in the case of the ingestion of pesticide residues in food where consumption patterns vary with age.

Introduction

Most long-term carcinogen bioassays are conducted by administering high doses of the test substance to animals at a constant rate for a large fraction of their natural lifetime.[1] Interpreting the results of these bioassays in a human context requires at least three types of extrapolation: from high experimental doses to low environmental doses; from animals to humans; and from constant dosing rates used in laboratory studies to intermittent or variable dosing patterns experienced by humans. In this paper, risk assessment methods that may be used in the last type of extrapolation are considered.

The effects of variable exposure will be examined within the context of the Armitage–Doll multistage model[2] and the Moolgavkar–Venzon–Knudson two-stage birth–death–mutation model.[3] The multistage model has been extended to the case of time-dependent dosing by Crump and Howe;[4] similar results for the two-stage model have been given by Thorslund et al.[5] In the "Models of Carcinogenesis" section, the mathematical development of these models is reviewed as described in Murdoch and Krewski,[6] with special emphasis on the importance of changes in tissue growth rates and cell kinetics over time.

There are many sources of temporal variability in human exposures. Occupational exposures may occur only in the workplace and for a small part of a person's working lifetime. Similarly, accidental exposures may be of very short duration. Dietary exposures to food additives and contaminants are dependent on consumption patterns that change with age, availability, and lifestyle.

The application of the risk assessment methods discussed here is illustrated in the "Applications" section, using two examples in which exposure patterns vary over time. The first example involves exposures of adult astronauts to volatile organics in a closed space station environment for a relatively short period of time. The second example focuses on dietary exposure to pesticide residues in children, which can differ notably from that of adults as a consequence of different dietary habits. This latter example will also be used to explore the effects of tissue development during childhood.

Models of Carcinogenesis

Multistage Model

The multistage (MS) model assumes that neoplastic transformation of a normal cell requires the occurrence in sequence of k biological events.[2] Crump and Howe[4] showed that under time-dependent dosing, the MS model predicts a cumulative hazard at time t of approximately

$$H(t)=\int_0^t \cdots \int_0^{u_2} \prod_{i=1}^{k} [a_i + b_i d(u_i)]\, du_1 \ldots du_k \qquad (1)$$

where the transition rates $a_i+b_id(u_i)$ $(i=1,\ldots k)$ are linear functions of the instantaneous dosing rate $d(t)$ at time t. The probability of developing cancer by age t is then

$$P(t)=1-exp[-H(t)] \qquad (2)$$

It follows from Equation 2 that $P(t) \approx H(t)$ when the cumulative tumor hazard is small.

One of the objectives of carcinogenic risk assessment is to estimate the excess cumulative lifetime risk because of a

particular time-dependent exposure pattern. The excess lifetime risk is defined as the risk in Equation 2 evaluated at that time t corresponding to the life expectancy of the species of interest (e.g., 70 years for humans), less the lifetime risk in the absence of exposure. In this article, we will approximate the excess lifetime risk by the corresponding excess cumulative hazard at time t.

Murdoch and Krewski[6] showed that when only one of the transition rates depends on the dose, the cumulative hazard function may be written in the following form:

$$H(t) = a(t)[1 + bd_t^*] \tag{3}$$

The cumulative hazard in the absence of dosing is represented by

$$a(t) = (t^k/k!) \prod_{i=1}^{k} a_i$$

and b is a constant measuring the effect of dosing on the dose-dependent stage in the model. The quantity

$$d_t^* = \int_0^1 d(tu) r(u;t) du \tag{4}$$

represents an equivalent constant dose which, if administered at a constant rate over the interval $[0,t]$, would result in the same cumulative hazard at time t. The relative effectiveness function $r(u;t)$ measures the relative effectiveness of dosing at time tu $(0 \le u \le 1)$.

In the MS model with k stages, where stage r is dose-dependent, the relative effectiveness function takes the form

$$r(u;t) = \frac{k! u^{r-1}(1-u)^{k-r}}{(r-1)!(k-r)!} \equiv r(u) \tag{5}$$

independent of t; the equivalent constant dose is given by

$$d_t^* = \int_0^1 d(tu) r(u) du \tag{6}$$

Murdoch[7] has defined relative effectiveness functions of the general form (Equation 3) with $r(u;t) = r(u)$ independent of t as scalable, since these models allow the cumulative hazard at different times to be calculated by simple rescaling. Scalable relative effectiveness functions require much less data to estimate nonparametrically than a general time-dependent relative effectiveness function.

Examples of the relative effectiveness function r(u) for the MS model with $k = 6$ and $r = 1,\ldots,6$ are shown in Figure 1. Note that when an early stage is dose-dependent, early exposures are more effective than late exposures. Conversely, late exposures are more effective when a later stage is dose-dependent.

In addition to the cumulative lifetime risk, it is of interest to determine the contribution of exposures occurring at different ages to lifetime risk. In this regard, the relative contribution to the lifetime risk (RCLR) of dosing at time t is defined by

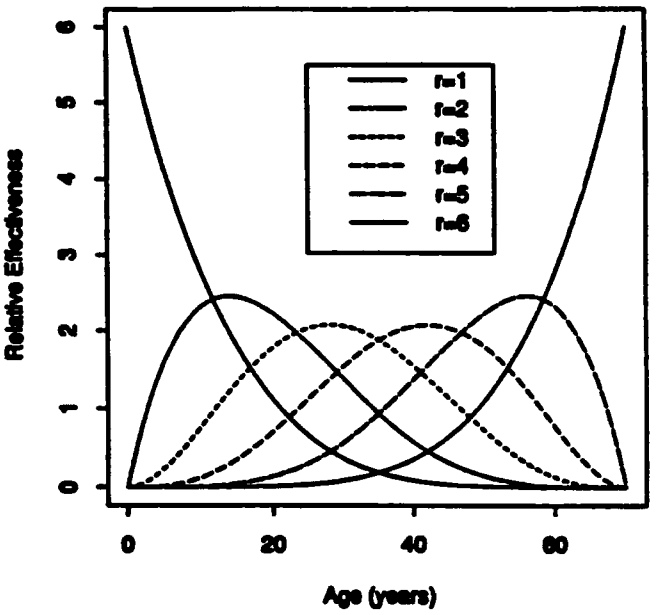

FIGURE 1. The relative effectiveness function $r(u)$ for the MS Model (with $k = 6$ stages, stage r dose-dependent and $t = 70$ years).

$$RCLR = d(tu) r(u;t) / d^*(t) \tag{7}$$

Note that the RCLR takes into account the effects of the level of both the level of exposure and the relative effectiveness of that exposure at each time t. Inclusion of the equivalent constant dose $d^*(t)$ in the denominator of Equation 7 renders the RCLR independent of the units in which dose is measured. Comparison of RCLR values at two different points in time reflects the relative contribution of exposures occurring at those times to lifetime risk.

Two-Stage, Birth–Death–Mutation Model

The two-stage, birth–death–mutation (BDM) model is similar to a MS model with $k = 2$, with explicit provision for the number $N(t)$ of normal stem cells at time t, and the net birth rate $\delta(t)$ of initiated cells which have undergone the first transformation.[8] Murdoch and Krewski[6] showed that when only one transition rate is dose-dependent, the cumulative hazard can be represented in the same form as Equation 3 with $a(t)$ and $d^*(t)$ defined in terms of the BDM model. Applications of the two-stage model in carcinogenic risk assessment have recently been reviewed by Krewski et al.[9] With the first stage dose-dependent, we have

$$r(u;t) = \int_u^1 f_{12}(u,u_2;t) du_2 \tag{8}$$

where: $f_{12}(u_1,u_2;t)=w(u_1,u_2;t)/k(t)$ (9)
$(0<u_1<u_2<1)$,

$$w(u_1,u_2;t)=N(tu_1)exp[r(tu_2)-r(tu_1)] \quad (10)$$

and

$$k(t)=t^{-2}\int_0^1\int_0^{u_2} w(u_1,u_2;t)du_1du_2 \quad (11)$$

The cumulative net birth rate of intermediate cells from time 0 to time t is represented by

$$r(t)=\int_0^t \delta(u)du$$

When the second stage is dose-dependent, then

$$r(u;t)=\int_0^u f_{12}(u_1,u;t)du_1 \quad (12)$$

Under the simplifying assumptions that $N(t) \equiv N$ and $\delta(u) \equiv \delta$ are constant, we have

$$r(u;t)=t\delta\frac{e^{(1-u)t\delta}-1}{e^{t\delta}-t\delta-1} \quad (13)$$

or

$$r(u;t)=t\delta\frac{e^{ut\delta}-1}{e^{t\delta}-t\delta-1} \quad (14)$$

when the first or second stage is, respectively, dose-dependent.[6] As indicated in Figure 2, early exposures are more effective than later exposures when the first stage is dose-dependent. Here, $t\delta$ represents the cumulative net birth rate of initiated cells per lifetime. When $t\delta = 0$, the relative effectiveness function is equivalent to that in a MS model with $k = 2$ and $r = 1$. Although the relative effectiveness function for the BDM model is bounded above by $t\delta$, information on the maximum biologically plausible value of δ is lacking.

While the assumptions that N(t) and $\delta(t)$ are constant expedite the mathematical analysis of the BDM model, these assumptions are oversimplifications of reality. Enesco and Leblond[10] found that the numbers of cells in most rat tissues increase with age up to approximately 34 to 48 days of age, at which point tissue size starts to stabilize.

In addition to increases in cell number (hyperplasia), tissue growth can occur as a result of an increase in cell size (hypertrophy). Although hyperplasia is primarily responsible for initial tissue growth, the rate of cell division decreases with age.[11] The development of tissues that are not self-renewing ceases when maturity is reached. Some tissues such as the brain are fully developed in early childhood, whereas others such as the skeletal system do not achieve maturity until after adolescence.

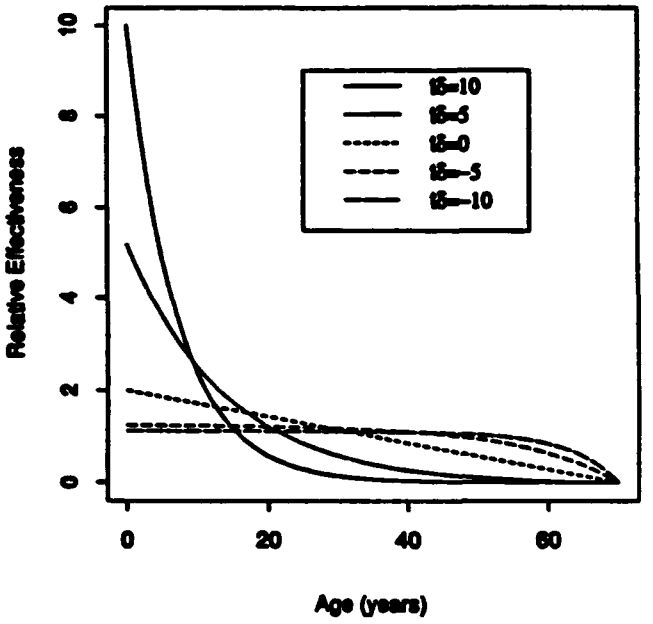

FIGURE 2. The relative effectiveness function $r(u;t)$ for the BDM model (with the first stage dose dependent and the cumulative net birth rate of initiated cells equal to $t\delta$ at $t = 70$ years).

Growth in cell mass can be assessed by comparing tissue weight to DNA content.[12] This approach to distinguishing between increases in cell number and cell size is difficult to apply in mammalian liver because of the formation of multinucleate cells as well as cells with single nuclei, but with diploid or tetraploid amounts of DNA (polyploidy).

Regarding $N(t)$ as the number of normal stem cells may also be an oversimplification. Moolgavkar and Luebeck[8] note that this is inconsistent with the assumption that mutation occurs during cell division, because the mitotic index (the per-cell rate of cell division) varies over time. For example, Ellwein and Cohen[12] report approximately 100 times higher mitotic indices in stem cells in week-old rats as compared with rats 8 weeks of age. The estimation of mitotic rates based on DNA incorporation of tritiated thymidine during cell division is discussed by Moolgavkar and Luebeck.[9]

When specific information on $N(t)$ is unavailable, a rough surrogate for the number of stem cells in the target tissue is gross organ weight. This latter indicator has the advantage of being readily available for humans but does not take into account hypertrophic effects or changes in mitotic indices with time.

In general, very little information is available about the kinetics of initiated cells as represented by their net birth rate $\delta(t)$. Initiation/promotion assays may provide some direct information on the birth and death rates of initiated cells. In the mouse liver system described by Pitot and Dragan,[14] foci thought to correspond to clones of premalignant initiated cells can be identified histologically. Such assays have been used

in liver, urinary bladder, and skin but are not well developed in other tissues. The statistical use of data on initiated cell kinetics in fitting the BDM model is discussed by Moolgavkar et al.[3] and Luebeck et al.[15]

Murdoch and Krewski[6] explored the results of assuming a constant rate of proliferation of intermediate cells, independent of age, while Krewski and Murdoch[16] assumed that the net birth rate was a constant multiple of the birth rate of normal cells. In this paper, we consider an intermediate approach with

$$\delta(t) = \delta_N(t) + \delta \qquad (15)$$

where: $\delta_N(t)$ = net birth rate of normal cells at time t calculated on the assumption that all changes in tissue weight are due to changes in cell number rather than cell size

δ = a constant representing the excess net birth rate of intermediate cells

This choice is based on the assumption that intermediate cells will respond to their microenvironment in essentially the same way as normal cells do but will be slightly more ($\delta > 0$) or less ($\delta < 0$) successful at proliferation. Under these assumptions, then

$$w(u_1, u_2; t) = N(tu_2)\exp[(u_2 - u_1)\delta] \qquad (16)$$

For illustrative purposes, assume that $N(t)$ is proportional to human liver weight, as shown in Figure 3. The fitted curve represents a continuously differentiable spline function[17] fit to the original data reported by Snyder et al.[18] The resulting relative effectiveness functions shown in Figure 4 are similar to those based on Equation 13 because the inclusion of the $\delta_N(t)$ term in Equation 15 tends to compensate for the variation in $N(tu_2)$ in Equation 16.

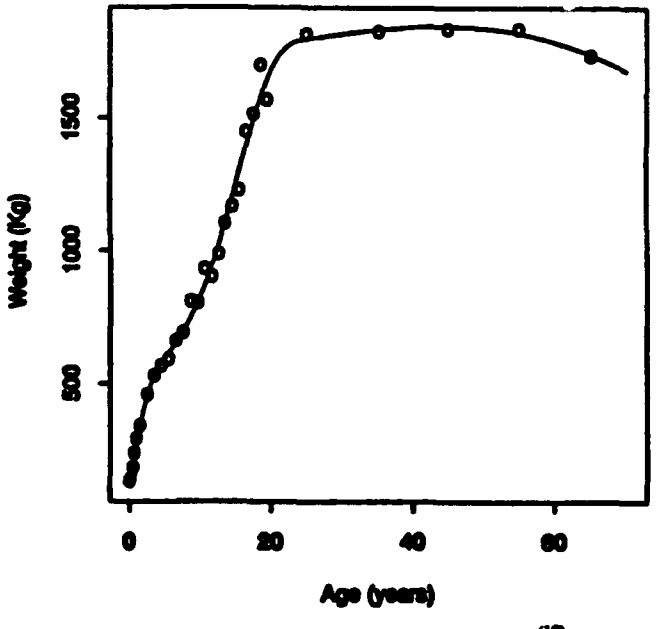

FIGURE 3. Human liver weight as a function of age.[18]

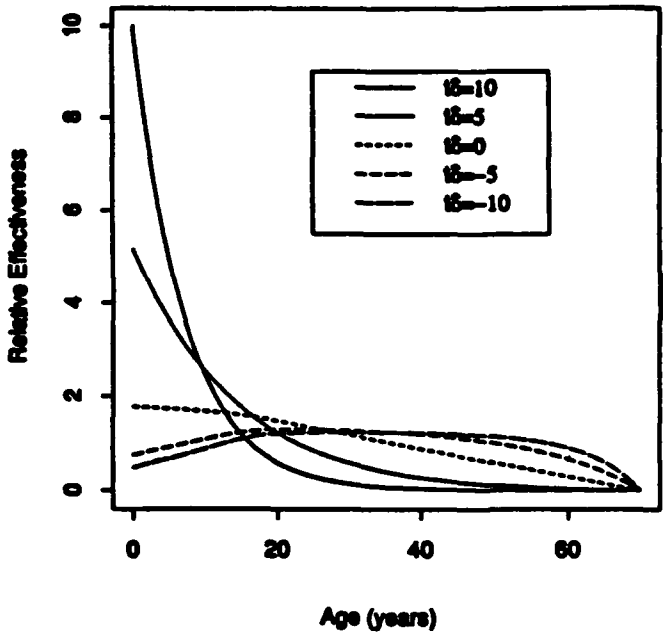

FIGURE 4. The relative effectiveness of time-dependent dosing in the BDM model (with the first stage dose dependent, $N(t)$ proportional to liver weight, $\delta(t)$ satisfying equation 15, and t = 70 years).

Applications

In this section, we indicate how the theoretical results presented in the "Models of Carcinogenesis" section may be exploited in two specific applications. The first example involves astronauts working in a space-station environment for a limited period of time and their exposure to chemical contaminants in the space-station atmosphere. In the second example, the impact of changes in tissue growth and cell kinetics on the potential risks of childhood exposure to pesticide residues in food are considered. Consideration is also given to the effects of changes in food consumption patterns with age.

Spacecraft Maximum Allowable Concentrations

The National Aeronautics and Space Administration (NASA) is planning to place a manned space station in Earth orbit by the mid-1990s. Because the space station is a closed environment, some contamination of its atmosphere is inevitable. Possible sources of contamination include off-gassing of cabin materials and metabolic waste products of crew members. Although most sources of atmospheric contamination will release only small amounts of chemical contaminants into the air, these contaminants may accumulate in the closed space-station environment.

The U.S. National Research Council[19] has been working with NASA to develop methods for establishing spacecraft maximum allowable concentrations (SMACs) for

space-station contaminants. Because astronauts will spend a maximum of 180 days in the space station during a single mission, there is a need to develop air quality guidelines that address these intermittent exposures.

Here, we focus on the question of establishing exposure guidelines for carcinogenic substances present in the atmosphere for astronauts working in the space station for periods of 180 days or less. Following the National Research Council,[19] we will assume that an astronaut would be at least 25 and at most 45 years of age at the start of the mission.

One approach to risk assessment with intermittent exposures is based on amortizing the total dose experienced during the time period of interest over a lifetime.[20] Risk estimates are obtained by multiplying the lifetime average daily dose (LADD) defined by

$$\bar{d}_t = t^{-1}\int_0^t d(u)du \qquad (17)$$

by a measure of carcinogenic potency derived from a laboratory bioassay with constant, daily, lifetime exposure. Except in very special cases ($r = k = 1$ in the MS model), the use of the LADD will not lead to the same risk as the lifetime equivalent constant dose (LECD) defined in Equation 4.

In the case of a single, linearly dose-dependent transition rate as considered in the previous section, the ratio of excess cumulative hazard due to the actual exposure experienced to the excess hazard based on dose amortization is

$$C = \frac{LECD}{LADD} \qquad (18)$$

calculated at the time t of interest.

The methods of the "Models of Carcinogenesis" section were used to calculate the correction factor C at age t=70 years for the MS model under the following assumptions.

- The age at the start of exposure is 25, 30, 35, 40, or 45 years.
- The duration of exposure is 1, 30, or 180 days.
- The number of stages in the model is $k = 1, ..., 6$.
- The dose-dependent stage is stage $r = 1,..., k$.

The values of C obtained under the above assumptions are shown in Table I for the case of a 30-year-old astronaut. These calculations reveal two important findings. First, there was almost no difference in the values of C for the different durations of exposure, when the other assumptions are held constant. This is *not* to say that the model predicts the same risk from 1 through 180 days' exposure, but rather that it predicts that the risk is very nearly proportional to the length of exposure period within this range. This follows from the fact that the $r(u;t)$ functions are rather smooth in the MS model, so that they are nearly constant over relatively short time intervals (6 months or less out of an expected lifespan of 70 years).

The second striking feature of these calculations was that the largest value of C was 2.06 (Table I). Even though the MS model with $k = 6$ may theoretically require correction factors of up to 6, these do not arise for dosing in mid-life. It should also be noted that the value of C can be as small as 0.09, indicating that the LADD can substantially overestimate the actual risk corresponding to the LECD. Since the purpose of the present analysis is to ensure protection of astronauts against increased cancer risks, we will focus our attention

TABLE I. Values of the Ratio C = LECD/LADD for the MS Model with Stage r of k Dose-Dependent for 30-Year-Old Astronauts

Stage Affected	Duration of Exposure	Number of Stages k					
r	(days)	1	2	3	4	5	6
1	1	1.000	1.143	0.980	0.746	0.533	0.365
	30	1.000	1.142	0.978	0.744	0.531	0.364
	180	1.000	1.136	0.968	0.733	0.520	0.355
2	1		0.857	1.469	1.679	1.599	1.371
	30		0.858	1.470	1.678	1.597	1.367
	180		0.864	1.472	1.672	1.583	1.348
3	1			0.551	1.260	1.799	2.056
	30			0.553	1.262	1.801	2.056
	180			0.560	1.272	1.806	2.052
4	1				0.315	0.900	1.542
	30				0.316	0.902	1.545
	180				0.323	0.916	1.561
5	1					0.169	0.578
	30					0.170	0.581
	180					0.174	0.594
6	1						0.087
	30						0.087
	180						0.090

primarily on upper, rather than lower limits of C.

The results presented in Table II indicate that these conclusions also hold for astronauts of different ages. Our calculations confirm that the upper bound on C of 2.06 from Table I holds under all of the conditions defined by the above assumptions.

Similar calculations were done for the BDM model under the following assumptions.

- The age at the start of exposure is 25, 30, 35, 40, or 45 years.
- The duration of exposure is 1, 30, or 180 days.
- The number of normal cells $N(t)$ is proportional to human liver weight (cf. Figure 3).
- The net birth rate follows Equation 15 with $t\delta = -10$, -5, 0, 5, or 10.
- The dose-dependent stage is stage $r = 1$ or 2.

The values of C tabulated in Table III indicate that the general conclusions reached with the MS model also hold for the BDM model. There is almost no difference in the values of C for the different durations of exposure, when all other factors are held constant; the value of C ranges from 0.016 to at most 1.4. Although the BDM models considered would admit values of C as high as 10, these do not arise under the relatively short-term, midlife exposures considered here.

Pesticide Ingestion by Infants and Children

Toxicological risk assessment procedures are intended to protect not only healthy adults in the general population but also susceptible population subgroups. The presence of Alar™ in apple products has recently focused attention on the potential risks of pesticide residues in the diets of infants and children.[21,22] This general issue is currently under investigation by the Committee on Pesticides in the Diets of Infants and Children within the U.S. National Research Council.[23]

Infants and children may be at greater risk than adults subjected to the same level of exposure on a body weight basis for several reasons. First, as noted in the "Models of Carcinogenesis" section, exposures occurring early in life are more effective than later exposures with an early stage carcinogen. On the other hand, adults may be at greater risk than children with a late stage carcinogen.

TABLE II. Values of the Ratio C = LECD/LADD for the MS Model with Stage r of k Dose-Dependent under Exposures of 30 Days' Duration Starting at Various Ages

Age (years)	Stage Affected	Number of Stages k					
	r	1	2	3	4	5	6
25	1	1.00	1.28	1.24	1.06	0.85	0.66
	2		0.72	1.38	1.77	1.90	1.83
	3			0.38	0.99	1.58	2.03
	4				0.18	0.59	1.13
	5					0.08	0.32
	6						0.04
30	1	1.00	1.14	0.98	0.74	0.53	0.36
	2		0.86	1.47	1.68	1.60	1.37
	3			0.55	1.26	1.80	2.06
	4				0.32	0.90	1.55
	5					0.17	0.58
	6						0.09
35	1	1.00	1.00	0.75	0.50	0.31	0.19
	2		1.00	1.50	1.50	1.25	0.93
	3			0.75	1.50	1.87	1.87
	4				0.50	1.25	1.88
	5					0.31	0.94
	6						0.19
40	1	1.00	0.86	0.55	0.31	0.17	0.09
	2		1.14	1.47	1.26	0.90	0.58
	3			0.98	1.68	1.80	1.54
	4				0.75	1.60	2.06
	5					0.54	1.37
	6						0.37
45	1	1.00	0.71	0.38	0.18	0.08	0.03
	2		1.29	1.36	0.98	0.58	0.31
	3			1.24	1.77	1.58	1.13
	4				1.07	1.90	2.03
	5					0.86	1.83
	6						0.66

TABLE III. Values of the Ratio C = LECD/LADD for the BDM Model with Exposures of 30 Days' Duration Starting at Various Ages

Stage Affected	Starting Age	Cumulative Net Birth Rate of Initiated Cells $t\delta$				
r	(years)	−10	−5	0	5	10
1	25	1.238	1.303	1.334	0.840	0.279
	30	1.238	1.280	1.184	0.577	0.137
	35	1.236	1.245	1.034	0.392	0.067
	40	1.227	1.195	0.863	0.264	0.032
	45	1.206	1.121	0.732	0.173	0.016
2	25	1.201	1.128	0.750	0.182	0.017
	30	1.222	1.199	0.902	0.277	0.035
	35	1.234	1.250	1.055	0.412	0.072
	40	1.242	1.287	1.209	0.606	0.148
	45	1.247	1.314	1.364	0.885	0.303

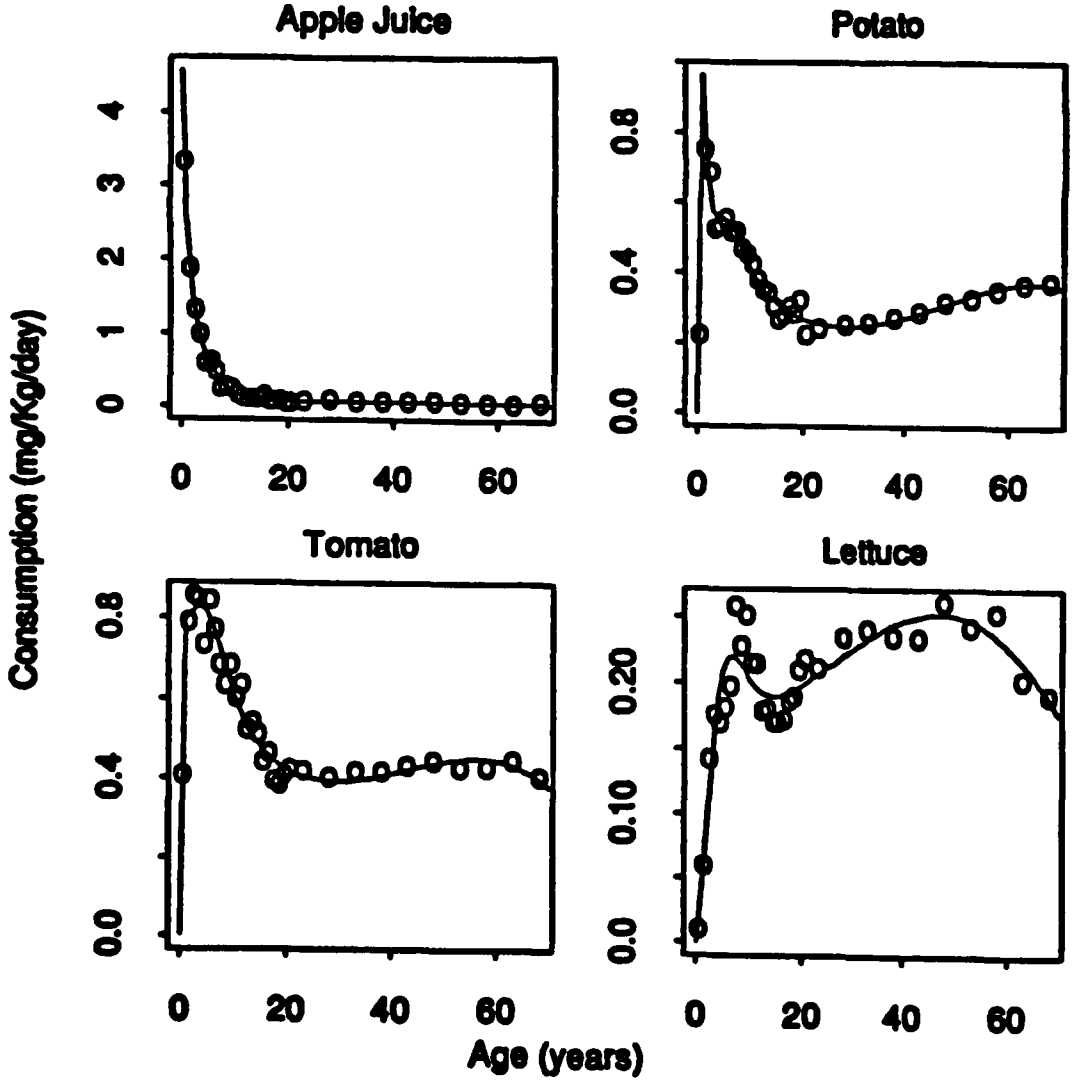

FIGURE 5. Consumption rates of apple juice, potato, tomato and lettuce by age.

Second, it is conceivable that perinatal tissues undergoing rapid growth and development may be more susceptible to carcinogenic stimuli than mature tissues. Empirical evidence on age-dependent physiological susceptibility is limited. Studies of the acute toxicity of pesticides have revealed mixed results. Gaines and Linder[24] found weanling rats more sensitive than adults to 4 of 28 pesticides tested, whereas 18 pesticides were more toxic to the adult. Assuming that cells undergoing mitosis are most vulnerable to genetic damage by DNA-reactive chemicals, there may be greater opportunity for genetic damage in developing tissues in which the rate of cell division is high. As the number of cells in the target tissue increases, however, the total number of cell divisions may also increase even if the mitotic index decreases.

Third, infants and children may be at greater risk than adults because of their different food consumption patterns. Dietary diversity increases with age; children consume far fewer foods than do adults. For example, fruits account for nearly 30% of the average non-nursing infant's diet[25] but a much smaller proportion of the average adult's diet. Because of their greater exposure to certain foods, children may be at greater risk than adults from pesticide residues present in these foods.

Here, we will restrict our attention to the impact of food consumption on potential risks associated with pesticide residues in food. Specifically, we calculate the correction factor C required to adjust estimates of risk based on average food consumption levels across all ages to reflect the greater consumption of certain foods by young people.

Wargo[26] conducted a detailed analysis of food consumption data from the 1977–1978 National Food Consumption Survey conducted by the U.S. Department of Agriculture.[27] As indicated in Figure 5, the consumption of apple juice is much greater among very young children than adults. The maximum consumption of potatoes and tomatoes occurs among children 1 through 6 years of age. The consumption of lettuce increases throughout childhood and is higher among adults than among children. These particular foods were chosen to illustrate a variety of food consumption patterns, including cases where childhood consumption is less than and greater than adult consumption.

Under the MS model, the value of the correction factor C varies from 0.27 to 3.74 for apple juice and from 0.79 to 1.33 for the other foods (Table IV). The fact that the largest values of C occur with apple juice is due to the temporal correspondence of the peak in consumption with a period of high relative effectiveness of dosing. Under the BDM model, the values of C ranged from 0.25 to 5.25 for apple juice and from 0.71 to 1.46 for the other foods (Table V).

The maximum values of C calculated here are notably larger than in the previous application to astronauts. The largest values of C under both the MS and BDM models occur when the first stage is dose-dependent. The values of C also

TABLE IV. Values of the Ratio C = LECD/LADD for the MS Model for Pesticide Residues in Apple Juice, Potato, Tomato, and Lettuce

Food	Stage Affected	Number of Stages k					
	r	1	2	3	4	5	6
Apple juice	1	1.00	1.64	2.23	2.77	3.27	3.74
	2		0.36	0.48	0.61	0.76	0.93
	3			0.30	0.34	0.38	0.43
	4				0.28	0.31	0.34
	5					0.27	0.30
	6						0.27
Potato	1	1.00	1.05	1.13	1.21	1.27	1.33
	2		0.94	0.90	0.90	0.94	0.99
	3			0.97	0.89	0.85	0.84
	4				1.00	0.92	0.86
	5					1.02	0.95
	6						1.04
Tomato	1	1.00	1.08	1.16	1.22	1.27	1.31
	2		0.92	0.94	0.97	1.01	1.06
	3			0.90	0.91	0.91	0.92
	4				0.90	0.91	0.90
	5					0.90	0.91
	6						0.90
Lettuce	1	1.00	0.95	0.90	0.85	0.82	0.79
	2		1.05	1.05	1.02	0.99	0.96
	3			1.05	1.09	1.07	1.04
	4				1.04	1.10	1.10
	5					1.03	1.10
	6						1.01

TABLE V. Values of the Ratio C = LECD/LADD for the BDM Model for Pesticide Residues in Apple Juice, Potato, Tomato, or Lettuce

Food	Stage Affected r	Cumulative Net Birth Rate of Initiated Cells $t\delta$				
		−10	−5	0	5	10
Apple juice	1	0.72	0.90	1.53	3.27	5.25
	2	0.39	0.36	0.32	0.28	0.25
Potato	1	0.94	0.96	1.04	1.26	1.46
	2	0.91	0.91	0.94	1.01	1.06
Tomato	1	0.97	0.99	1.07	1.26	1.39
	2	0.92	0.91	0.91	0.90	0.89
Lettuce	1	1.03	1.01	0.96	0.83	0.71
	2	1.05	1.05	1.06	1.03	0.97

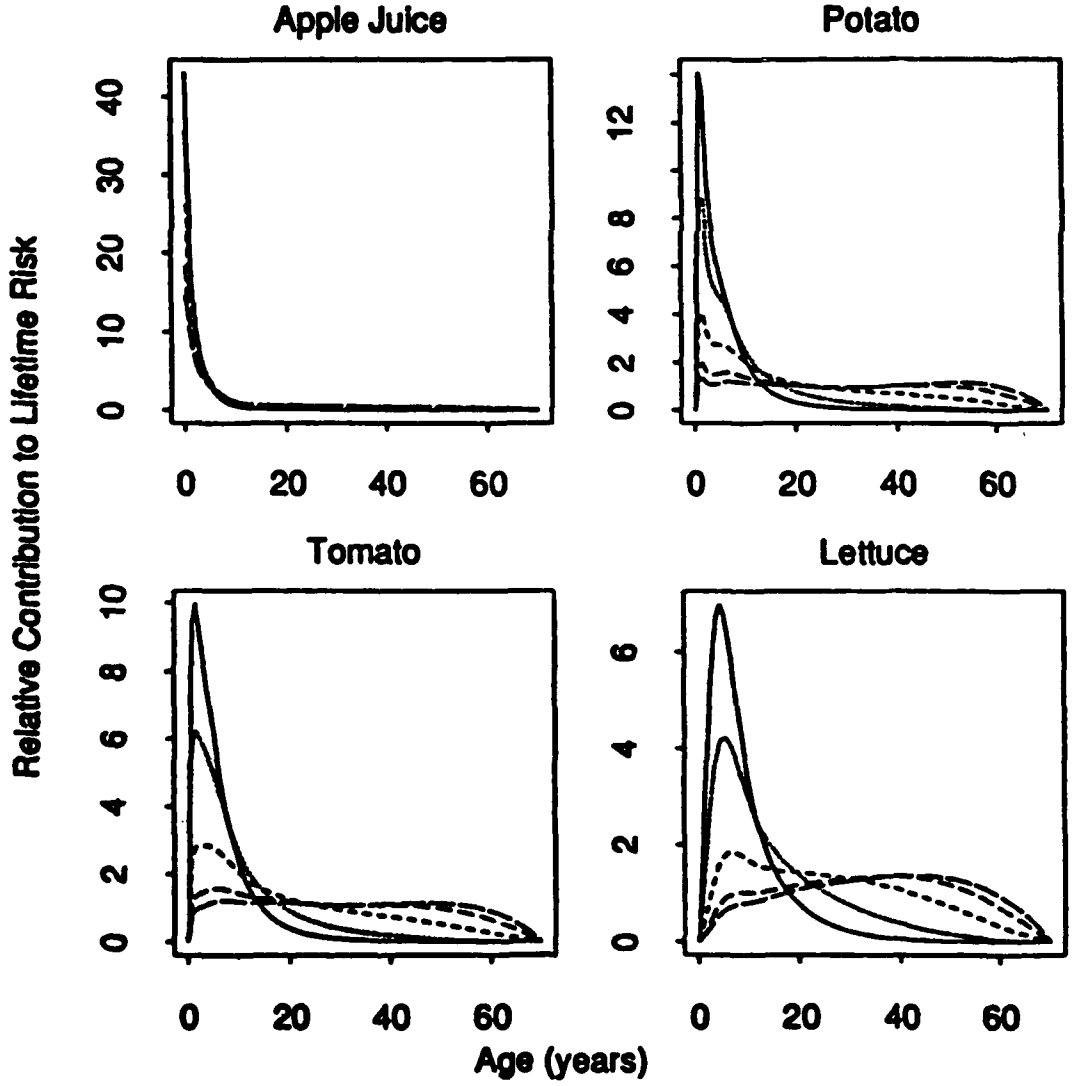

FIGURE 6. Relative contributions to lifetime risk of exposures at different ages in the BDM model (with the first stage dose dependent, $N(t)$ proportional to liver weight, $\delta(t)$ satisfying equation 15 and t = 70 years; line types are as in Figure 4.)

increase in the MS model with the number of stages k and in the BDM model with the cumulative net birth rate of initiated cells t.

Figure 6 depicts the relative contribution to the excess cumulative hazard at age 70 of the exposures at earlier ages for the BDM models with the first stage dose-dependent. The largest contributions to the cumulative hazard occur during childhood, when the relative effectiveness of dosing is highest. This is particularly true for apple juice, since the period of highest consumption also occurs early in life.

Summary and Conclusions

In this paper, we have considered approaches to estimating the lifetime risk associated with intermittent or time-dependent exposures to carcinogenic substances. One method is to amortize the cumulative dose equally over a lifetime, giving the lifetime average daily dose or LADD.

The concept of relative effectiveness of dosing at different points in time was used to determine a lifetime-equivalent constant dose or LECD, which yields the same lifetime risk as the actual time-dependent exposure pattern. Although the LADD generally will not lead to the same lifetime risk as the LECD, it is possible to bound the error in predictions of risk based on the LADD under specific assumptions concerning the process of neoplastic transformation. Under the classical Armitage–Doll multistage model, the actual risk will exceed the prediction of risk based on the LADD by a factor of at most k, the number of stages in the model. Since the corresponding bound for the two-stage, clonal, expansion model is proportional to the proliferation rate of initiated cells, greater errors may accrue when initiated cells proliferate rapidly.

The universal upper bounds derived for the MS and BDM models may be improved upon in specific applications. For astronauts exposed to atmospheric contaminants in a closed space-station environment for periods of up to 6 months, the LADD can underestimate the lifetime cancer risk by a factor of about twofold or less under the MS model. (This occurs because of the limited effectiveness of dosing in midlife under the MS model.) In practice, this can be accomodated by increasing estimates of risk based on the LADD by an adjustment factor of two. The adjustment factor required under the BDM model is even smaller, being less than 1.4 in all cases considered.

The error associated with estimates of risk based on the LADD in other situations may exceed the twofold bound established for astronauts. This occurred in our second example involving dietary exposure to pesticide residues in food. On a body-weight basis, children consume far greater amounts of some foods than do adults. For example, one-year-olds consume more than 30 times the amount of apple juice per kg body weight per day than do adults. With an early-stage carcinogen for which the relative effectiveness of dosing is highest early in life, the use of an average level of food consumption across all ages in risk assessment may lead to underestimates of risk for this food by a factor of about fivefold under the models and assumptions employed here.

These results indicate that accurate estimates of carcinogenic risk require detailed information on the temporal patterns of exposure. Knowledge of the mechanism of carcinogenesis, such as whether an agent is an early or late-stage carcinogen, and the growth kinetics of normal and initiated cells, is also important in evaluating the relative effectiveness of exposures at different points in time. Although of fundamental importance in carcinogenesis, relatively little information is available on the mitotic indices of stem cells and the birth and death rates of initiated cells: the impact of the simplifying assumptions made here and elsewhere in the absence of such information remains to be explored. In the interim, it is still possible to place plausible upper bounds on the error in estimates of risk based on the lifetime average daily dose as was attempted in the two applications considered here.

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Carcinogenic Risks of Polycyclic Organic Matter (POM)

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Many combustion emissions and related complex mixtures containing polycyclic organic matter (POM) are carcinogenic to humans. A comparative potency method has been developed to estimate the human cancer risk from POM sources. This method involves evaluating the tumorigenic potencies of POM from the selected source in relation to other POM sources that have been shown to cause lung cancer in humans. The mouse skin tumor-initiation bioassay provides the best correlation with the human cancer unit risks for emission sources where quantitative epidemiological results are available. The comparative potency method is presented together with the data developed to test the underlying constant relative potency hypothesis. This hypothesis has been validated for POM from coke ovens, roofing coal tar, and cigarette smoke by comparing the relative lung cancer potency in humans to the relative tumor initiation potency in mouse skin.

The carcinogenic risks of POM from a series of emission sources were determined using the comparative potency method. This method was first used to estimate the lung cancer risk for diesel and gasoline vehicle emissions and has now been extended to a series of POM sources including woodstove emissions, residential oil furnace emissions, aluminum smelter emissions, and ambient air particles. The lifetime cancer risk/μg extractable organic matter/μm^3 ranges over nearly two orders of magnitude (100-fold) and is similar to the range in potency for the organic matter emitted from the three human carcinogens to which these sources are compared. The human carcinogens range from 9.3×10^{-4} cancer risk/g extractable organic matter/m^3 for coke oven emissions to 2.2×10^{-6} for cigarette smoke. When the cancer unit risk is expressed as μg particulate matter/m^3, the range in potency is reduced to one order of magnitude.

Introduction

In the early 1900s, the first chemicals recognized to be human and animal carcinogens were complex mixtures of coal tars and coal soot from chimneys.[1] Fractionation and animal bioassay of these mixtures resulted in the identification of carcinogenic polycyclic organic matter (POM).[2,3] POM is a general term referring to a complex mixture of polycyclic aromatic compounds including many diverse classes of hydrocarbons (e.g., polycyclic aromatic hydrocarbons, [PAHs]), substituted aromatic hydrocarbons (e.g., nitrated-PAH), and heterocyclic aromatic compounds (e.g., aza-arenes). The earliest recognized sources of carcinogenic POM were derived from coal-related processes, particularly combustion; however, POMs are emitted from the combustion of petroleum (e.g., diesel and gasoline fuel), wood, and synthetic chemicals (e.g., plastics). Although several carcinogenic PAH species are known to account for a significant portion of the cancer risk associated with POM from coal tar soot[1,2] and some petroleum combustion emissions, PAHs do not account for all the carcinogenic activity of several other POM sources (e.g., diesel emissions, urban aerosol).[3,4] Scientific consensus working groups considering the use of benzo[a]pyrene (B[a]P) as a marker of cancer risk concluded that B[a]P alone is not a good surrogate for PAH, POM, or cancer risk.[5] Recent improvements in quantitative chemical analytical detection methods for measuring POM species have shown that B[a]P is not always well correlated with total PAH content and that many other carcinogenic chemicals, such as other PAHs, substituted PAHs (e.g., nitro-PAH), aromatic amines, and aza-arenes, are present in complex POM mixtures.

The primary source of POM in air pollution is from combustion of fossil fuels (e.g., coal, oil, gasoline, diesel fuel), vegetative matter (e.g., wood, tobacco, biomass), or synthetic chemicals (e.g., municipal and hospital wastes, hazardous waste, plastic waste). These products of incomplete combustion have generally been referred to as PICs, and the cancer risk from PICs are thought to arise primarily from POM (the polycyclic organic matter generally associated with the particle or soot component of the PIC). The carbonaceous soot particles emitted from combustion sources contain most of the POM component that induces tumors in animals and mutations in cells and has been clearly implicated in epidemiological studies as a human carcinogen.[6,7] Incomplete combustion products, however, also contain gaseous chemicals that are carcinogenic, such as benzene,

This report has been reviewed by the Health Effects Research Laboratory, U.S. EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. EPA.

TABLE I. Cancer Unit Risk Estimates Based on Human Epidemiological Data and Used in the Comparative Potency Method

Emission Source	POM Unit Risk: Best Estimate Lifetime Risk/μg Organic Matter/m^3 (Lower Limit–Upper Limit)
Coke oven	9.3×10^{-4} (5.0 to 15.0×10^{-4})*
Roofing tar (coal)	3.6×10^{-4} (1.0 to 7.2×10^{-4})
Cigarette smoke	2.2×10^{-6} (2.2 to 3.7×10^{-6})

*From Albert et al.[13] who based the coke oven unit risk estimate on the U.S. EPA report "The Carcinogen Assessment Group's Carcinogen Assessment of Coke Ovens," OHEA-C-81-018, U.S. Government Printing Office, 1982. In 1989, the U.S. EPA CRAVE Work Group reviewed, verified, and published in the Integrated Risk Information System (IRIS) a revised coke oven unit risk of 6.2×10^{-4} based on the Agency's 1984 Carcinogen Assessment of Coke Oven Emissions.[10] For the purposes of this paper, the original estimate of 9.3×10^{-4} is used to be consistent with the publications on which this report is based.

aldehydes, and alkenes (e.g., 1,3-butadiene), and semivolatile organic compounds which have not been well characterized either chemically or toxicologically.

The complexity of the POM emissions, estimated to contain thousands of chemicals, has precluded the quantitative cancer risk assessment of these emissions based on analysis of its components. Because human exposure to these POM emissions occurs as the whole complex mixture, both qualitative assessment [6–9] and quantitative assessments of the human cancer risks[10] have been based on either the whole emissions (PIC) or the POM component.

Recently, Thorslund[11] has proposed the use of a method that could be described as a "B[a]P equivalents factor approach" based on assessing the risks from mixtures containing PAHs by comparing the relative carcinogenic potency (in rodents) of several individual PAHs to the carcinogenic potency of B[a]P to determine the potency of each PAH relative to B[a]P. These relative potencies (B[a]P equivalents) are then multiplied by the concentration of the individual PAHs in the mixture and summed to estimate the total cancer risk. This approach would underestimate the risk if any other carcinogenic components are present. It may be particularly useful for simple PAH mixtures or for those complex mixtures where it can be demonstrated that the PAH component accounts for the carcinogenicity of the whole mixture. One disadvantage of this approach is that there is not direct evidence for the human carcinogenicity of the individual PAH.

The comparative potency method for cancer risk assessment of POM mixtures described in this report relies on both epidemiological data resulting from human exposure to the whole mixture and tumor initiation potency resulting from treatment of mouse skin with the extractable organic matter (EOM) from the emissions.

What Is the Comparative Potency Method?

The comparative potency method for human cancer risk assessment of complex mixtures of POM is a method for estimating human cancer risk when there are no human cancer data for the specific POM mixture being assessed, but there are human cancer data for a similar POM mixture.[12–15] The human cancer risk of the unknown mixture is estimated by using the relative bioassay potency of the unknown mixture and known human carcinogen multiplied by the human potency of the known human carcinogen. The underlying assumption in this method is the constant relative potency hypothesis described in the following section.

The Constant Relative Potency Hypothesis

The comparative potency method is based on the hypothesis that there is a constant relative potency across different bioassay systems (e.g., human and rodent), where relative potency is determined by the ratio of the slopes of the dose responses from the same bioassay, as shown below:

$$\text{relative potency} = \frac{\text{bioassay potency of carcinogen}_1}{\text{bioassay potency of carcinogen}_2}$$

The bioassay potency for each POM emission source is determined from the slope of the dose–response curve. Several methods for estimating this slope have been examined for mutagenicity bioassays[16] and the mouse skin tumor assay.[17,18] The general expression for the constant relative potency hypothesis for estimating human cancer potency is the following:

$$\frac{\text{relative human potency}}{\text{relative bioassay potency}} = (k)$$

The human cancer potency has been determined using the linear, nonthreshold, extrapolation model and is expressed as the individual lifetime excess lung cancer risk from continuous exposure to 1 $\mu g/m^3$ inhaled air.[13] The human cancer potencies (lung cancer unit risks) for the three known human carcinogens are shown in Table I.

The constant relative potency assumption is implicit in any comparison that utilizes the relative toxicity of two substances in animals to estimate their relative toxicity in humans. This constant relative potency assumption is an

experimentally testable hypothesis if the relative potency of two mixtures or components in one bioassay (e.g., humans) can be determined and compared to the relative potency in a second bioassay. The test of this hypothesis is whether there is a constant relationship (k) between the relative potencies in the two bioassays being compared. The current limitation to our testing of this hypothesis is the availability of human lung cancer data for quantitative estimation of the human cancer risk. Research is now in progress to expand the human database to include at least one additional human carcinogen, smoky coal combustion emissions.[19] The human cancer potency estimate will be based on a highly exposed population of women in China who are exposed indoors to smoky coal emissions and have a high lung cancer rate.[20]

Testing and Validation of the Constant Relative Potency Hypothesis

This hypothesis was initially tested for three complex POM emissions from a coke oven, roofing coal tar pot, and cigarette smoke by using the human lung cancer data from epidemiological studies of humans exposed to these emissions, as shown in Table I. The relative human cancer potency, as expressed by lung cancer unit risks, was compared to the potency of these emission sources in a series of bioassays.[12,13,16] Human lung cancer unit risk estimates; animal tumorigenicity data; and short-term, mutagenesis bioassay data were developed for each of these emission sources.[13,16,17] The relative bioassay potency for several of these bioassays is shown in Table II, where the ratio of the dose–response slopes for each of the POM emission sources listed was normalized to (divided by) the coke oven emissions within each bioassay. The potency of these three POM emissions in the mouse skin tumor-initiation assay resulted in the highest correlation across these three human carcinogens. Although further research on this methodology is continuing using additional human data[19,20] for current applications of the comparative potency method, the mouse skin tumor-initiation assay is proposed as the only bioassay that produced a constant relative potency across the coke oven, roofing tar, and cigarette smoke emissions adequate to support the assumptions in the comparative potency method.

The validity of this constant relative potency hypothesis may depend on the chemical nature of the mixtures being compared and the similarity of those mixtures. Characterization of the POM from these three emission sources identified a wide range of polycyclic aromatic[21] compounds. In general terms, these POM mixtures are similar in their relatively high content of polycyclic aromatic compounds. All of the mixtures contain PAHs; however, the relative concentration of these PAHs differ substantially among the mixtures. The coke oven emissions and cigarette smoke contain mutagenic basic constituents containing nitrogen; however, the specific nitrogen heterocyclic compounds are different in these two mixtures and the roofing coal tar emissions do not contain these nitrogen bases.[3]

Another approach to evaluation of this method is to compare the cancer unit risk estimates obtained by the comparative potency method to risk estimates obtained by species extapolation from chronic, lifetime, animal inhalation studies. The comparative potency method predicted a human lung cancer unit risk for diesel emissions that is very similar to the unit risk estimate for the same diesel vehicle used in a lifetime, rodent inhalation, carcinogenesis study.[22] A more recent extrapolation from three rodent inhalation studies[23] resulted in unit risk estimates similar to those obtained in the comparative potency method. These two independent approaches to the cancer risk estimation of the POM from diesel emissions results in very similar cancer unit risk estimates.

Application of the Comparative Potency Method

The first application of this method to the estimation of the human lung cancer unit risk was for the POM associated with diesel particle emissions.[13] The cancer unit risk for the diesel emissions was determined based on the relative potency of the diesel POM compared to each of the human carcinogens (e.g., coke oven emissions) as shown below:

$$\text{Diesel risk} = \text{Coke oven risk} \times \text{Relative potency [Diesel} \div \text{Coke oven]}$$

The average unit risk for the most potent diesel sample across three comparative human carcinogens was 4.4×10^{-4} lifetime risk/μg organic matter/m^3 (3.5×10^{-5} risk/μg particle/m^3).

TABLE II. Comparison of Relative Potencies of the Human Carcinogens in Several Bioassay Systems*

	Human Lung Cancer	Tumor Initiation	Mammalian Cell Mutation	Microbial Mutation TA98 (+MA)
Coke oven topside	1.0	1.0	1.0	1.0
Roofing (coal) tar	0.39	0.20	1.4	0.78
Cigarette smoke	0.0024	0.0011	0.066	0.52

*All of the bioassay potencies[13] for each emission is compared (normalized) relative to coke oven emissions.

TABLE III. Cancer Unit Risk Estimates for POM and Particulate Matter from Typical Combustion Sources as Determined by the Comparative Potency Method[A]

Emission Source	POM Unit Risk (lifetime risk/μg organic matter/m^3)	Particle Unit Risk (lifetime risk/μg particulate matter/m^3)
Automobile, Gasoline		
Catalyst[4,13]	4.2×10^{-5}	1.8×10^{-5}
Noncatalyst[4,23]	1.1×10^{-4}	1.6×10^{-5}
Automobile, Diesels[13,23][B]	2.3×10^{-4}	2.6×10^{-5}
Trucks, Diesel[4,13]	6.6×10^{-6}	1.8×10^{-6}
Woodstove, soft wood[13,23]	2.7×10^{-5}	1.0×10^{-5}
Aluminum smelter	9.1×10^{-4}	1.1×10^{-5}
Residential oil[4]		0.9×10^{-5}
Air particle extract[23][C]	1.3×10^{-4}	

[A]Based on comparing the relative mouse skin tumor-initiation potency of the POM from particle emissions from these sources to the relative human lung cancer unit risks for POM emissions with human epidemiological data (coke ovens, roofing tar [coal], and cigarette smoke).
[B]Average of two light-duty diesel vehicles.
[C]Containing ambient woodsmoke (64%) and mobile source emissions (36%).[23]

Two other light-duty diesel vehicles had very similar unit risks of 1.3 and 1.2×10^{-4}/μg organic matter/m^3 (2.3 and 2.0×10^{-5}/μg particle/m^3).[13]

Comparison of the mutagenic potency of a series of POM from diesel and gasoline vehicle emissions in *Salmonella typhimurium* with the tumorigenic potency showed high correlations between the two bioassays.[4] Both the tumorigenic potencies and the mutagenic potencies of this series of diesel and one gasoline emission engine were also highly correlated with the concentration of nitrated PAH and PAH in the POM mixture.[4] This provides further evidence that the chemical similarity of these automotive emissions may justify the extension of the use of the short-term mutagenicity bioassay to estimate the comparative human risk of automotive emissions that can be shown to be substantially similar chemically. In Albert et al.,[13] several short-term bioassays, which were all highly correlated with the tumor initiation potency[16] for this series of automotive emissions, were used to estimate the human lung cancer unit risks. In order to use the relative potency in mutagenicity bioassays to predict the relative potency in the mouse skin tumor assay, the constant relative potency hypothesis was tested and the proportionality constant (k) used in the comparative potency method was determined.[15] An adequate database comparing the mouse skin tumor potency to the mutagenicity potency are necessary in order to extend this method to the use of short-term bioassays to estimate relative potency. Only in the case of this series of automotive emissions has such a validation of the comparative potency method for short-term bioassays been accomplished.[4,15]

Since the initial application of the comparative potency method to the estimation of cancer unit risks for diesel emissions, new studies of other POM-containing emissions have been conducted.[4] Mouse skin, tumor-initiation, dose–response studies of additional automotive emissions (e.g. noncatalyst, leaded gasoline emissions), woodstove emissions, residential oil combustion, urban air particle extracts, and aluminum smelter emissions have been completed. Using the relative potencies in the mouse skin tumor-initiation assay, the lung cancer unit risk has been estimated for these POM emission sources, as shown in Table III. These unit risks range from 9.1×10^{-4} to 6.6×10^{-6}, a range similar to the range of unit risks for the three carcinogens used in the comparative potency method. If the human cancer risk is expressed as risk per μg of particulate matter per cubic meter of inhaled air, rather than per μg organic matter (e.g., POM), then the lung cancer risks for many of these sources are remarkably similar, and the range in potency is reduced from two orders of magnitude difference for the organic matter to one order of magnitude difference between different sources for the particulate matter.

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Issues Surrounding Comparative Risk Assessements of Operational Materials: An Example with Air Force Hydraulic Fluids

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New products entering today's marketplace frequently undergo toxicity testing to determine the potential risks they pose to exposed people. Not uncommonly, these products undergo more extensive testing than materials that have been in use, are often products intended for the same end use, and may have completely different toxicity profiles in test animals. Differences in the nature of the products, the amount of toxicity data available, and differing target tissues for the materials complicate comparisons of the potential human health hazards of various products. Especially difficult interpretive issues arise when new products cause effects in experimental animals that, for compelling biological reasons, are not expected to occur in humans or other primates. Some of these issues in comparative health risk assessment of new materials are highlighted by Air Force-sponsored studies of a candidate nonflammable hydraulic fluid based on polychlorotrifluoroethylene oligomers. This material has performance characteristics similar to hydrocarbon- and phosphate ester-based fluids that are currently in use.

Introduction and Background

Polychlorotrifluoroethylene (PolyCTFE) 3.1 oil is a candidate base stock for a nonflammable hydraulic fluid under consideration by the United States Air Force for use in advanced aircraft. No current hydraulic fluid is nonflammble; hydraulic fluid fires have resulted in the loss of a number of aircraft in the past. In addition to reducing the risk of aircraft fires, PolyCTFE 3.1 oil possesses performance advantages for high-pressure systems. As part of the process to evaluate this new fluid as a replacement for current hydrocarbon-based hydraulic fluids, the Air Force entered upon an extensive research program to determine the potential toxicity associated with its use. The conduct of this research provides a useful example of an integrated toxicology program. *In vivo*, *in vitro*, and computer modeling resources were combined to provide rapid insight into the nature and severity of toxic effects observed in experimental animals and to simultaneously provide an assessment of the relevence of the toxicity to humans.

PolyCTFE oligomers were previously regarded as "biologically inert." The 3.1 oil has very low acute toxicity after oral ingestion (rat $LD_{50} > 9.2$ g/kg), inhalation exposure ($LC_{50} > 2.0$ mg/L in rats), or application to the skin (dermal $LD_{50} > 3.7$ g/kg). PolyCTFE 3.1 oil is not a skin irritant, causes minimal eye irritation, and has only mild potential for skin sensitization.[1]

In a 90-day inhalation study with the 3.1 oil,[2] groups of ten male or ten female rats were exposed to airborne concentrations of PolyCTFE 3.1 oil of 250, 500, or 1000 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. All rats gained weight, but weight gain was reduced in rats at the highest concentration. Liver weight increased for both male and female rats with increasing dose of PolyCTFE 3.1 oil. Reduced weight gain and increased liver weight were more marked in male than in female rats.[2] Repeated exposure to 3.1 oil also resulted in slower oligomer excretion than observed after a single 6-hour exposure. The slower rate of excretion after repeated exposure appeared to be due to accumulation in body fat. The fat has a high storage capacity for PolyCTFE oligomers based on tissue/blood partition coefficients of 400 for trimer and 750 for tetramer.[3]

At necropsy, the liver was greatly enlarged with a variety of changes in cellular structures. Liver cells from the 500 and 1000 mg/m^3 PolyCTFE 3.1 oil exposure groups were two to three times larger than cells from control rats. In hepatocytes from exposed rats, there was an increase in number of peroxisomes in liver cells. Rats exposed to 500 mg/m^3 3.1 oil were held for up to 1 year after the end of the 90-day exposure to determine how quickly the liver effect resolved. At day 105 postexposure, the liver was only minimally improved; at day 236 postexposure, livers were still not normal, but the size of the cells had decreased to near control. At 1 year postexposure, the livers were relatively normal, indicating liver toxicity of 3.1 oil is only slowly reversible in rats.[2] No other organs were significantly affected and, even at the 1000 mg/m^3 concentration, no rats died from the exposures. Repeated oral-dosing with Halocarbon 27S, a higher-average

molecular weight PolyCTFE oligomer, caused similar toxic changes in the livers.[4] Peroxisome increases in rats have been associated with liver cancer in rats.[5–7] There is no evidence that such chemicals cause liver cancer in humans.

The results of this 90-day study were of concern for two reasons. First, liver effects were seen even at the lowest dose tested. Second, industrial hygiene data from an actual hydraulic fluid test system[8] found air concentrations of PolyCTFE 3.1 oil of approximately 100 mg/m^3 in a worker's breathing zone sample taken in a small room, and more than 250 mg/m^3 during a system leak. The fact that occupational exposures could be produced on the same order as exposures producing toxic effects in the animal studies led us to focus our laboratory's resources on elucidating the hazard potential. In addition, the effects in rats were only very slowly reversed after exposure.

A number of similarities were noticed between the effect of PolyCTFE 3.1 oil and perfluorodecanoic acid (PFDA), a compound previously studied in our laboratory.[9–11] Based on these observations and the expected omega oxidation route of n-alkane metabolism, it appears that PolyCTFE oligomers are converted to acids in the liver and that the acid was responsible for the toxicity.[12,13]

Methods

Hazard Assessment Studies

A decision tree paradigm was used to determine the relevance to humans of the liver toxicity in rodents (Figure 1). The working hypothesis related toxicity to formation of PolyCTFE oligomer-induced toxic acid metabolite in the liver. The no-effect-exposure concentration in different animals should be approximately equal to a nontoxic tissue dose of acid metabolites. The primary question was whether PolyCTFE was expected to be toxic in primates. If PolyCTFE was not mutagenic and not toxic in primates, then a guideline could be proposed based on a no-effect level in rodents. A series of studies was designed to test this hypothesis and answer the questions raised by the decision paradigm in order to assess the potential hazard of PolyCTFE 3.1 oil to humans. The studies used were 1) No Effect Study, 2) Mutagenicity, 3) Acid Toxicity Study, 4) Physiologically Based Pharmacokinetic Modeling, 5) Primate Studies, 6) Comparative Study of PolyCTFE Formulations, and 7) Comparison to Operational Hydraulic Fluids.

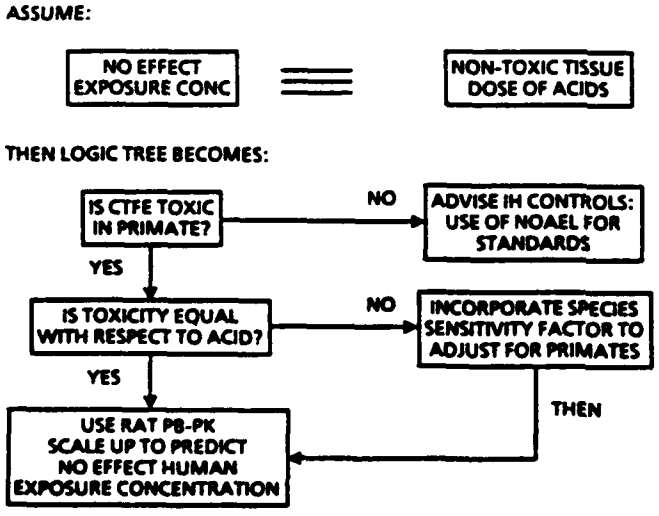

FIGURE 1. Decision tree for PolyCTFE risk assessment.* The first "NO" pathway leading to "ADVISE IH CONTROL" was proposed due to species differences in toxicity. (*for no mutagenicity — no initiation potential.)

Test Material

The candidate hydraulic fluid is a PolyCTFE mixture consisting of low-molecular-weight oligomers. The formulation of interest is a mixture of oligomers blended to obtain a viscosity of 3.1 centistokes/g at 100°C. PolyCTFE samples were analyzed using a gas chromatograph (Model 3700, Varian Instrument Group, Palo Alto, California) equipped with an electron capture detector. The PolyCTFE chromatograph shows two primary groups of peaks: the first is the trimer group containing three monomeric units with C_6 as the major component; the second set of peaks is the tetramer group containing four monomeric units with C_8 as the major component (Figure 2). The 3.1 oil hydraulic fluid contained 1.0% (v/v) of a rust inhibitor additive, neutral barium dinonylnaphthalene sulfonate. A second additive was 0.05% (v/v) of a proprietary antiwear compound. Hazard assessment studies were conducted using PolyCTFE without the rust inhibitor and antiwear additives.

PolyCTFE 3.1 oil was developed as a replacement for current hydraulic fluids. Differences between these hydraulic fluids and PolyCTFE 3.1 oil were not known. Current hydraulic fluids, MIL-H-5606 and MIL-H-83282, had not been studied under repeated dosing exposure conditions. Phosphate ester hydraulic fluids had only limited repeated dose studies. In addition, a low-temperature version of MIL-H-83282 (LT 83282) was developed as a replacement for MIL-H-5606. Three fluids, MIL-H-5606, MIL-H-83282, and LT 83282, all have hydrocarbons as their base stock. MIL-H-83282 has a trimer polyalphaolefin as the base stock, whereas LT 83282 has a dimer/trimer blend of polyalphaolefin as the base stock. MIL-H-5606 fluid is a naphthalinic-based stock.

Results

No Effect Study

A second 90-day inhalation study was conducted to determine a no-effect level for PolyCTFE by inhalation.[14] Ten male rats per group were exposed at 10, 50, and 250 mg/m^3 PolyCTFE 3.1 oil, 6 hours/day, 5 days/week for 13

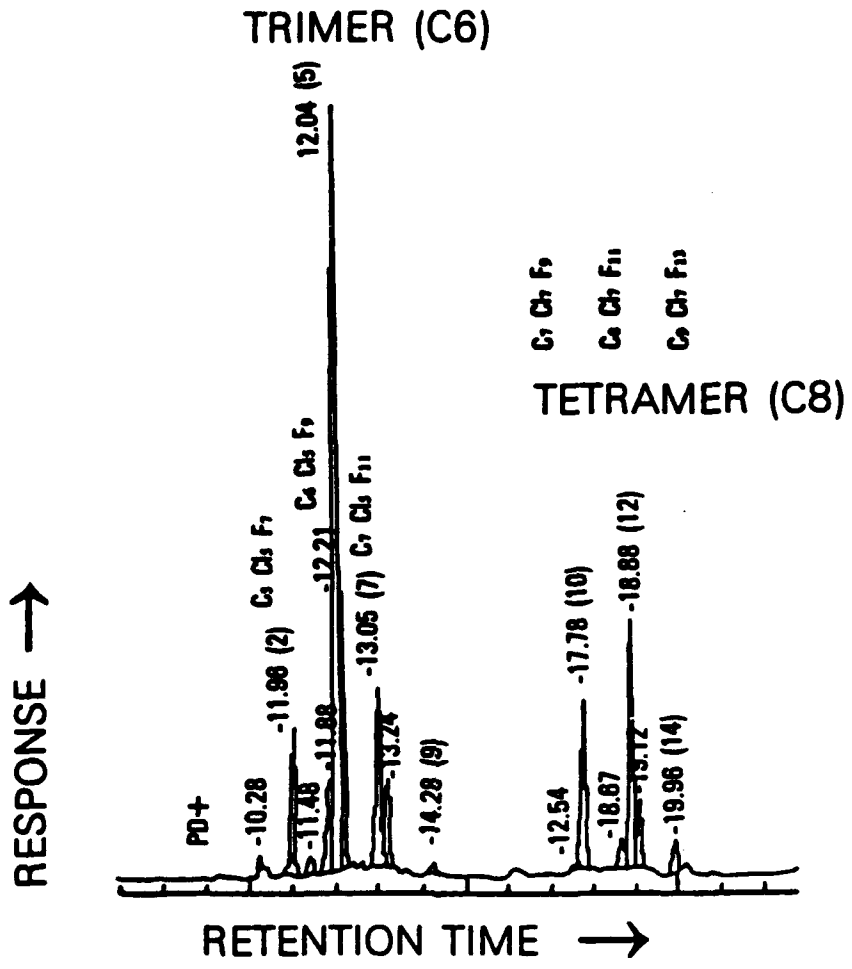

FIGURE 2. Gas chromatography trace of PolyCTFE 3.1 oil showing the trimer group (C_6) and tetramer group (C_8) of oligomers.

weeks. Female rats were not exposed in this study because they were observed to be less sensitive than males in the first 90-day study. PolyCTFE without any additives was used in this study to determine if the additives have an affect. The 250 mg/m^3 dose was repeated in order to confirm the effects in the first study.

Statistical analysis of the weekly body weights for all five doses of PolyCTFE (both 90-day studies), including both sets of control and 250 mg/m^3 values, revealed no differences between control and exposed animal weights. Rats exposed at 1000 mg/m^3 showed the smallest increase in body weight resulting in the lowest terminal body weight of all the groups. When the actual mean weight gains were calculated and analyzed, statistical differences were found at various time points for 250, 500, and 1000 mg/m^3. Mean-weight-gain data showed that there was no effect at the 10 and 50 mg/m^3 concentrations.[14]

Liver/body weight ratios were also analyzed collectively for both 90-day studies. The liver to body weight ratio at 50 mg/m^3 was the only parameter at this concentration that was statistically greater than values for control rats. Although livers examined histologically and by transmission electron microscopy (TEM) were not identical to control livers, the differences seen at the 50 mg/m^3 dose were not adverse. Also, there were no changes seen by TEM between control rat livers and livers from rats exposed at 10 mg/m^3 for 90 days.[14]

The number of peroxisomes per electron microscopic photograph (30,000X enlargements) was counted to quantitate peroxisomal proliferation (Figure 3). The 250 mg/m^3 dose resulted in essentially the same number of peroxisomes in hepatocytes as in the first study. The number of peroxisomes was not statistically greater than control numbers until the 250 mg/m^3 dose, although there was a trend toward increases in number of peroxisomes at the two lower concentrations.[14]

To further quantitate peroxisomal proliferation, beta-oxidation rates (Figure 4) representing the activity of the enzymes in peroxisomes were determined. The enzyme activity was statistically increased at 10 mg/m^3 PolyCTFE 3.1 oil. This was the only parameter in which a significant increase was found at the lowest dose. Data were not collected for 50 mg/m^3.[14]

At the 250 mg/m^3 dose, clinical chemistry analysis revealed statistically significant increases in plasma alkaline phosphatase and blood urea nitrogen (BUN). There were no changes in clinical chemistry parameters at the two lower doses.[14]

Mutagenicity Assays

PolyCTFE 3.1 oil was assessed for mutagenicity using the following assays: Ames *Salmonella* reverse mutation, hypoxanthine guanine phosphoribosyltransferase (HGPRT) locus Chinese hamster ovary (CHO) gene mutation, CHO/sister-chromatid exchange (SCE) and chromosome aberration, BALB/c-3T3 cell transformation, and *in vivo/in vitro* unscheduled DNA synthesis (UDS).[15] All were conducted both in the absence and presence of S9 fraction microsomal enzymes.

The results of the genetic tests indicate that PolyCTFE 3.1 oil has no significant interaction with genetic material.

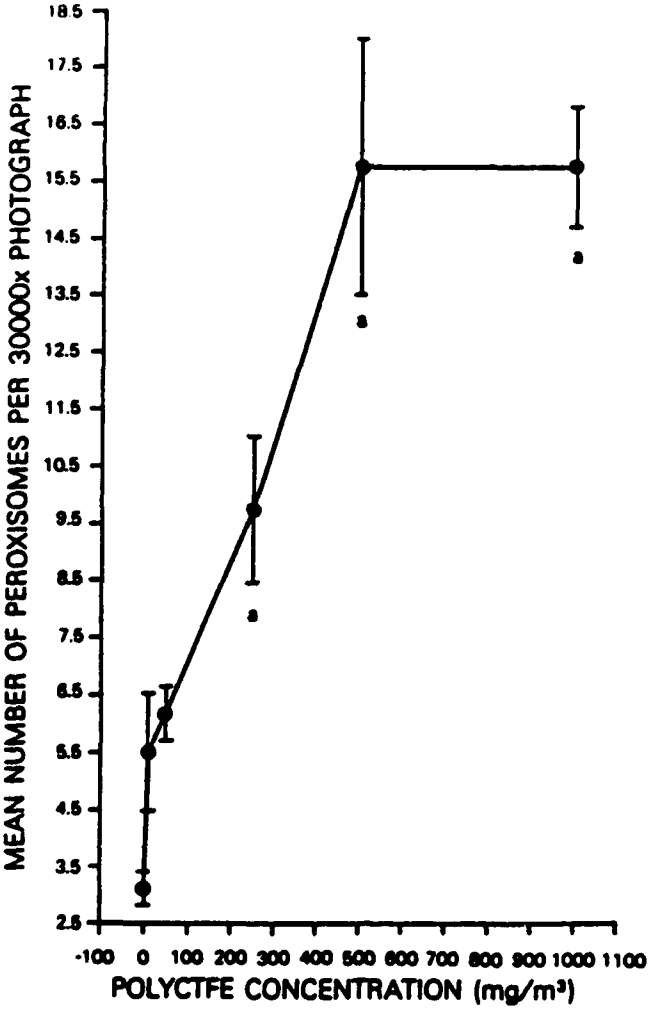

FIGURE 3. Mean number of peroxisomes per electron micrograph from livers of rats exposed to 0, 10, 50, 250, 500, or 1,000 mg/m^3 PolyCTFE for 90 days. *Legend:* a = significantly different than control at $p < 0.05$.

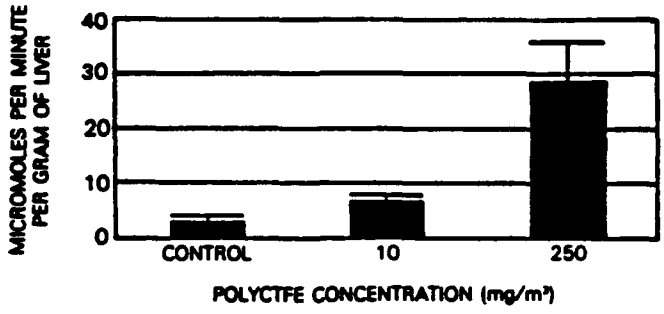

FIGURE 4. Mean beta-oxidation rates of peroxisomes from livers of rats exposed to 0, 10, or 50 mg/m^3 PolyCTFE for 90 days.

The results were negative for five of the six genetic end points. The HGPRT locus CHO gene mutation assay gave equivocal results without S9 but was negative with S9.[15]

Both the PolyCTFE trimer and tetramer acids were evaluated in the same assays as the 3.1 oil with the exception of the BALB/c- 3T3 cell transformation assay which was not conducted for the acids. PolyCTFE acids were negative in all tests conducted for assessing genotoxic activity.[16]

PolyCTFE Acid Study

The toxicity of PolyCTFE acids was examined by determining the LD_{50} for trimer and tetramer acids. The trimer acid LD_{50} was the same in male and female rats (396 mg/kg). The tetramer acid LD_{50} in male rats (88 mg/kg) was much lower and similar to the toxicity of PFDA. The toxicity of the tetramer acids on female rats (352 mg/kg) was only slightly less compared to the trimer acids. Sex differences were also noted in the toxicity of PFDA.[17] When rats were dosed weeky at the LD_{10} for 12 months, only the tetramer acids caused an increased liver weight and liver pathology.[13]

Physiologically Based Pharmacokinetic Model

An important part of the investigation of PolyCTFE 3.1 oil toxicity was the development of a physiologically based pharmacokinetic (PBPK) model from the rodent 90-day experiments.[3] The primary biological determinants of the disposition of PolyCTFE were blood:air and fat:blood partition coefficients, rates of metabolism, and pulmonary absorption. Metabolism of PolyCTFE by end-group oxidation produces the toxic acid species and fluoride ion that can both be readily detected. In rats, the values for these model parameters (Table I) provided a good description of kinetics of the trimer and tetramer under various inhalation exposure conditions (Figure 5).

The rat model was used as the basis for scale-up to create and test a similarly structured model for oral dosing with PolyCTFE in monkeys.[18] The scaled-up model was then used to estimate the appropriate dose levels for the primate studies. The model parameters (Table I) for the monkey produced a good description of the overall kinetic profiles in

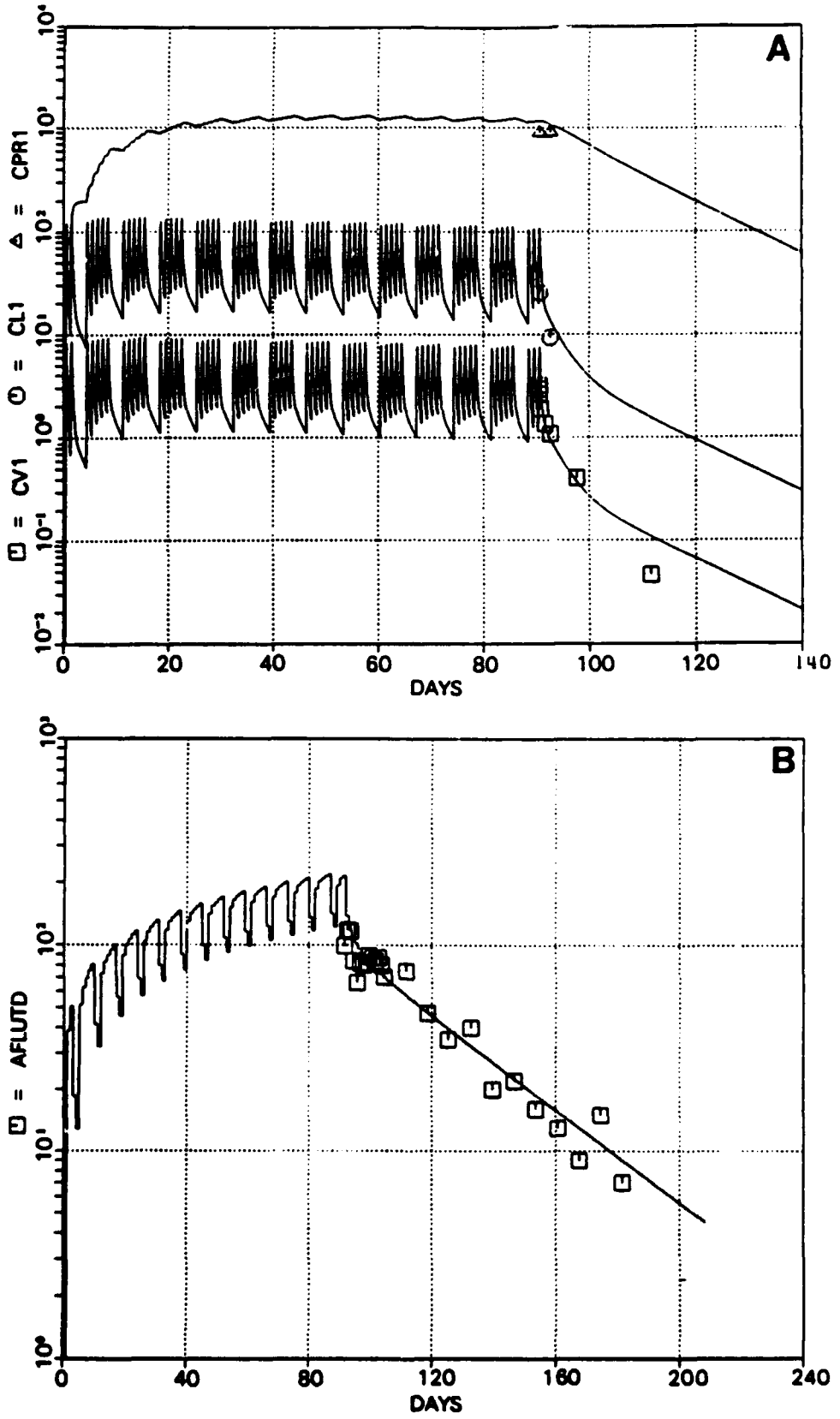

FIGURE 5. PB-PK Model results for PolyCTFE 3.1 oil for the rat based on a repeated inhalation dose of 0.5 mg/L (500 mg/m^3). Graph A: CPR1 is perirenal fat, CL1 is liver, and CV1 is venous blood (mg/L). Graph B: AFLUTD is urinary fluoride (mg/day), representative of metabolism.

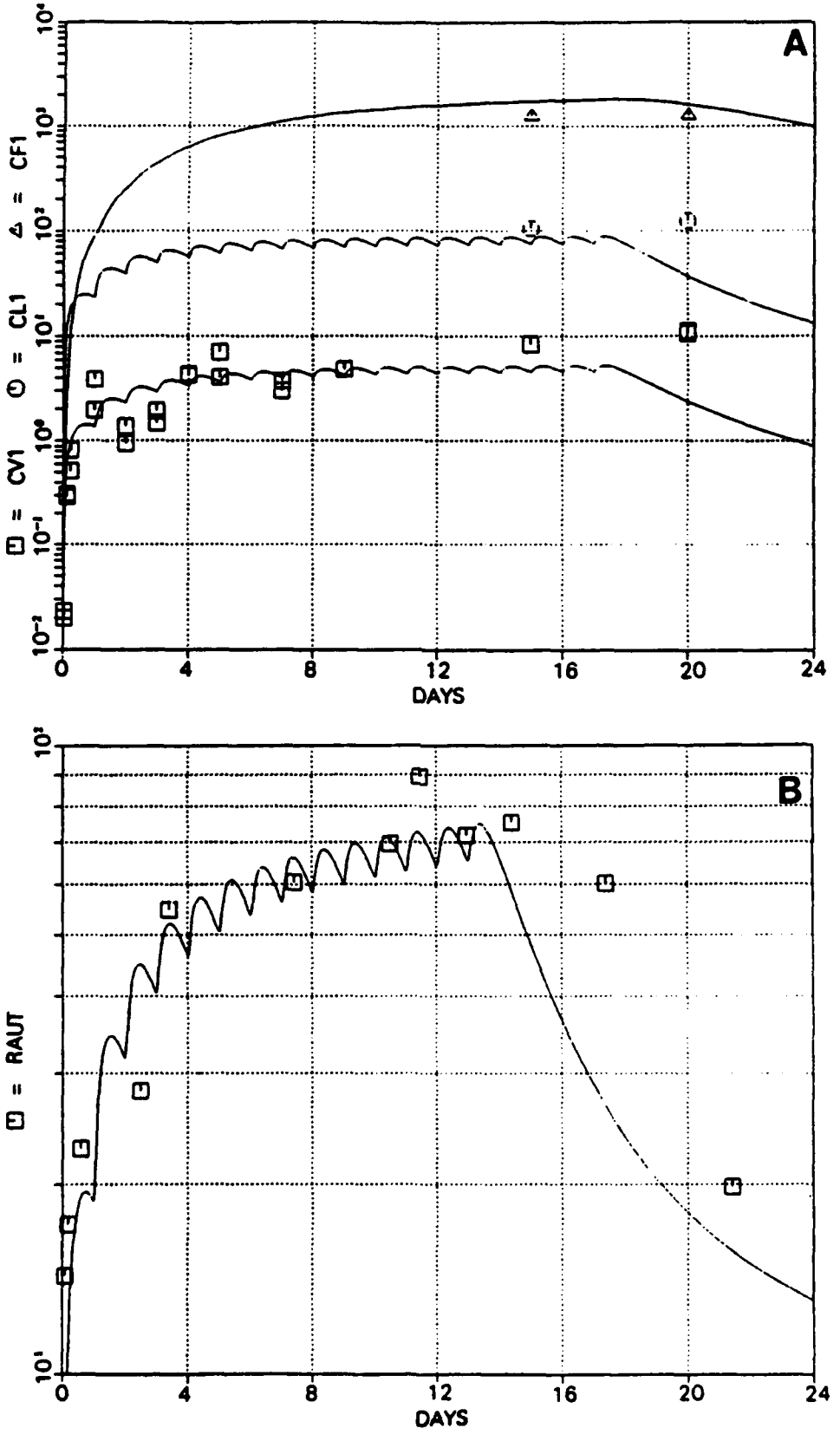

FIGURE 6. PB-PK Model results for PolyCTFE 3.1 oil for the primate based on a repeated oral dose of 0.725 g/kg Graph A: CF1 is perirenal fat, CL1 is liver, and CV1 is venous blood (mg/L). Graph B: RAUT is urinary fluoride (mg/day), representative of metabolism.

TABLE I. Parameter Values Used in PBPK Models for PolyCTFE Trimer and Tetramer in Rats and in Primates

Parameter	Rats (Inhalation)		Primates (Oral)	
	Trimer	Tetramer	Trimer	Tetramer
Partitions:				
Blood/air	33	35	33	35
Fat/blood	400	750	400	750
Rate of metabolism[A]	2.0	1.0	2.0	1.0
Relative % absorbed	—	—	9.2	9.2

[A]Per hour, for a 1 kg animal, adjusted allometrically by body weight (BW) to the negative one-third power, i.e., rate (hr^{-1} = 2.0 • $BW^{-1/3}$).

this second species by another route of administration (Figure 6). To obtain these curves, the absorption was set to be less than 10%. PolyCTFE does not appear to be well absorbed from the gastrointestinal tract in monkeys based upon actual data and the model. Development of the model will continue with the addition of compartments for the acid metabolites in order to provide a more quantitative comparison of risks across species than could be performed at this time.

Primate Studies

The concern with using PolyCTFE 3.1 oil is whether humans are at risk of liver toxicity from a chemical that causes peroxisomal proliferation in rats. Primates are usually insensitive to the liver toxicity associated with chemicals that cause peroxisomal proliferation in rats.[6] To better estimate the relevance to humans, monkeys were dosed once every 3 weeks (two monkeys for 421 days) or daily for 15 days (four monkeys). Pharmacokinetic measurements were made on the monkeys dosed for 421 days. Histopathology, including electron microscopy, was conducted on monkeys dosed for 15 days[19] and 421 days.[20]

Both the parent trimer and tetramer were excreted in the urine of monkeys. In contrast, very little tetramer was detected in rat urine. Clinical chemistry measurements appeared normal. There was no increase in the number of peroxisomes in liver cells or in peroxisomal enzyme activity. Although there were minor structural changes seen in the primate liver cells, the changes were not the same as those caused by PolyCTFE 3.1 oil in rat liver cells.[19]

The concentration of trimer and tetramer acid was low in primates in the 15-day study, while the concentration of tetramer acid was five times greater than parent tetramer in the liver of exposed rats (Figure 7). Examination of geometric means of the C_8:C_6 ratios also shows that the tetramer is highest in the livers of both species (Figure 8). The ratio is lower in the urine of primates than in the urine of rats, indicating that the rat clears the more toxic oligomer less efficiently.

To confirm that primate liver cells do not respond to PolyCTFE acids, primate hepatocytes were treated with trimer and tetramer acid *in vitro* under the same conditions as rat hepatocytes. Rat and primate hepatocytes were exposed to 50 µg/ml of either C_6 or C_8 PolyCTFE acid for 96 minutes. Peroxisomal beta-oxidation increased in rat hepatocytes but not in primate hepatocytes (Table II).[21]

Comparative Study of Formulations

Two comparative studies were conducted in rats. The ojective of the first study was to compare the relative toxicity of different PolyCTFE oligomers and different PolyCTFE formulations.[22] Rats were dosed orally for 14 days with 1.25 g/kg of pure oligomer (trimer or tetramer) or one of two 3.1 oil formulations. Body weights, liver weights, liver pathology, and liver enzyme activity were measured to assess the degree of toxicity.[22]

The tetramer was toxic, whereas the trimer had little toxicity. The standard 3.1 oil formulation of PolyCTFE consisting of trimer and tetramer in a ratio of 55:45 produced toxicity similar to the pure tetramer. The 3.1 oil formulation of PolyCTFE consisting of trimer and high-molecular-weight

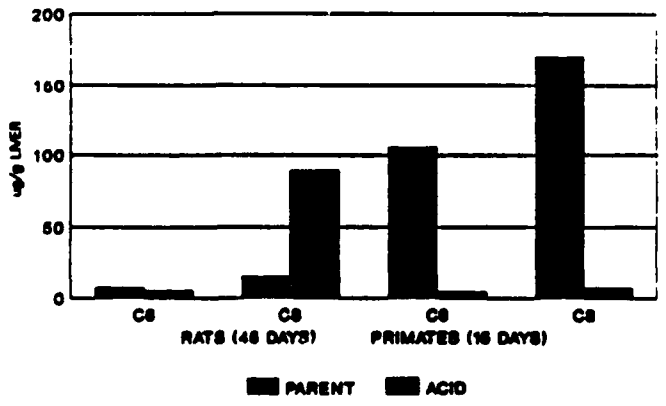

FIGURE 7. Concentration of PolyCTFE oligomers (parent) and acid in the liver of rats and primates.

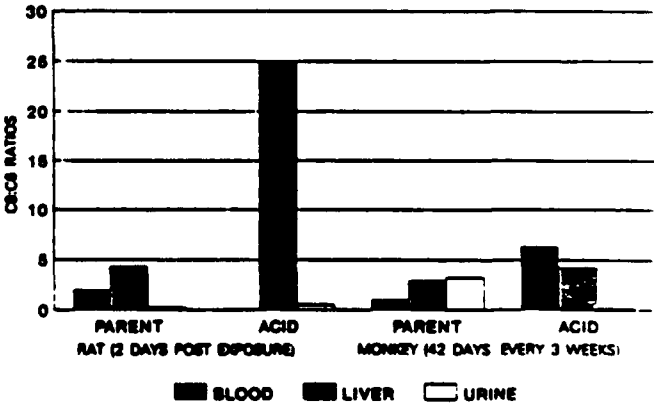

FIGURE 8. Geometric means of C_8:C_6 ratios for PolyCTFE oligomers (parent) and acid in blood, liver, and urine of rats and primates.

TABLE II. *In vitro* Comparison of beta-Oxidation of Primary Rat and Primate Hepatocytes After Exposure at 50 μg/ml PolyCTFE Acids for 96 Minutes

	(nM/min/mg)	
	Rat	Primate
Control	ND[A]	ND
C_8 Acid	13.2 ± 7.7[B]	ND
C_9 Acid	11.3 ± 5.3	ND

[A]Not detectable. Limit of detection = 3 nM/min/mg.
[B]Values represent the mean and standard deviation from three experiments with triplicate plates for each treatment group.

oligomers in the C_{10} range or greater in a ratio of 95:5 produced toxicity similar to pure trimer.[22]

Comparison to Operational Hydraulic Fluids

The second comparative study examined differences between hydraulic fluids in current operational use and PolyCTFE 3.1 oil.[23] Four male rats per fluid were dosed orally with 1 g/kg/day for 4 weeks. The fluids tested were PolyCTFE, a phosphate ester (PE), MIL-H-83282, MIL-H-5606, and a low temperature version of MIL-H-83282 (LT 83282).

PolyCTFE 3.1 oil and the PE killed three of four rats although the dose was cut in half after the third week. A second study with four male rats/fluid was conducted. The rats dosed with PE and PolyCTFE 3.1 oil were given 0.5 g/kg in the second study. Rats dosed with 0.5 g PolyCTFE 3.1 oil/kg survived except one rat developed a back problem and was sacrificed prior to the end of the study. One rat died from dosing with MIL-H-5606 in each of the studies. The rats appeared to be more susceptible to dosing problems with MIL-H-5606 than with the other fluids tested.[23]

Both PolyCTFE 3.1 oil and PE depressed weight gain in rat. MIL-H-5606 also depressed weight gain at times throughout the second study. Weight gain was normal for the 83282 fluids or even higher than control weights. Liver and relative liver weights were increased for MIL-H-5606, PE, and PolyCTFE 3.1 oil. Relative spleen weights were also increased by PE while the 3.1 oil caused an increase in kidney, relative kidney, testes, and relative spleen weights.[23]

All of the fluids caused an increase in urinary protein. MIL-H-83282 caused an increase in plasma alkaline phosphatase. An increase in white blood cell count and anemia (decreases in hemoglobin parameters) were seen for LT 83282. Persistent diuresis and a decrease in the number of lymphocytes was found for MIL-H-5606. Exposure to PE resulted in decreased BUN and creatinine, diuresis, and anemia (decreases in hemoglobin parameters). PolyCTFE 3.1 oil decreased plasma chloride and increased plasma proteins, liver enzymes (ALT, AST), and alkaline phosphatase. The 3.1 oil also caused a reversible diuresis and an anemia (decreased RBC and hemoglobin parameters).[23]

Only PolyCTFE 3.1 oil produced the same liver lesion seen after inhalation exposure. Liver perox-isomal beta-oxidation enzyme activity was elevated above control rates for all hydraulic fluid-exposed rats. A comparison of both studies revealed that liver peroxisomal beta-oxidation enzyme activity was comparable for all hydraulic fluids even though the PolyCTFE and PE groups received only half the dosage in the second study. More protein (hyaline droplets) accumulated in the kidneys of rats exposed to hydraulic fluids than the background level of controls. The protein accumulation in the kidneys of rats exposed to MIL-H-5606 was severe, whereas the rating for the other hydraulic fluids was mild.[23] A subsequent dose–response study of MIL-H-5606 with male rats dosed daily for 2 weeks revealed an increase in protein droplet accumulation in the kidney at a concentration as low as 0.1 g/kg (unpublished data).

Discussion

Pre-Use Toxicity Testing of Chemicals

The increasing public concern about the toxic effects of manmade chemicals has increased expectations regarding the level of toxicity information that should be available before new materials are put into use. These expectations have been given the form of law, both in OSHA's Hazard Communication Standard and in the requirements under the Toxic Substances Control Act (TSCA) for Premanufacturing Notifications on new products. At the same time, new products are being put on the market at an unprecedented rate. These combined pressures demand a new approach to chemical risk assessment that provides greater use of short-term test strategies, mechanistic studies, and computer analysis with less reliance on the traditional, animal-intensive, long-term studies.

Chemical Risk Assessment Approaches

Chemical risk assessment for commercial products is an extremely complex process. First, a hazard assessment for a given chemical is performed by extrapolating the results of animal toxicity studies. The most enduring challenge for the toxicologist is the quantitative interpretation of animal toxicity results to predict the potential for human harm. This human hazard assessment must be combined with an estimate of the potential exposure of people to the chemical or material in the specific situation of concern — termed the exposure assessment. Combining the hazard assessment for the chemical with the exposure estimate produces an overall risk assessment. Considering this estimated risk together with other costs and potential benefits to select the most acceptable alternative for a specific scenario is termed risk management.

Each step in this process is fraught with uncertainty. As a result, both state and federal regulatory agencies have

generally employed extremely conservative approaches, with multiple safe-sided assumptions and safety factors. In recent years, however, there has been growing recognition that extremely conservative risk estimates are unrealistic. A more pragmatic approach is needed, particularly in the case of chemicals that produce carcinogenic effects in animals which are of questionable relevance to humans. Such an approach would attempt to balance a quantitative estimate of potency with a qualitative assessment of the likelihood that the chemical is truly hazardous to humans. The difficulty, of course, is that the deficiencies in the current, conservative, risk assessment approach do not by themselves provide a justification for simply reducing current risk estimates. There has to be a scientific basis for obtaining more accurate estimates to ensure that the new estimates can be defended and that the assumptions and uncertainties involved in the risk assessment process can be documented and improved by data collection where possible.

Hazard Assessment Studies

Although the liver/BW ratio was increased at 50 mg/m^3 in the second 90-day study, TEM did not identify any adverse changes. This concentration was considered a no-observed-adverse-effect level (NOAEL). The no-observed-effect level (NOEL) was 10 mg/m^3 which was confirmed by transmission electron microscopy. The peroxisomal enzyme data in Figure 4 shows equivocal support for the NOAEL and NOEL. It is not known what the enzyme data means in terms of classic toxicity. Ruben and Wagner[24] discussed the concept of functional change versus a toxic change. Elcombe and Styles,[25] based on *in vitro* studies of human liver cells, found that humans are insensitive to liver growth parameters such as an increase in peroxisomes. They felt that the use of peroxisomal proliferation data (and related tumor data) may be inappropriate to assess human hazard.[25] The increase in peroxisomal enzyme activity may represent a functional change in the liver and not a toxic change at the lower concentrations. In support of this concept are the data showing that beta-oxidation by peroxisomes in hepatocytes from rats exposed to 250 mg/m^3 increased in response to PolyCTFE 3.1 oil and returned to control levels 60 days postexposure.[14] The relevance of peroxisomal proliferators to human liver cancer[5-7] and the concept of a functional change versus a toxic change[24] are both major issues today in the field of toxicology.

An erratic response to PolyCTFE 3.1 oil, observed for mutagenesis (without S9 only) at the HGPRT locus in CHO cells, was too tenuous to warrant any consideration in risk assessment.[15] This is supported by the fact that the trimer and tetramer acids were negative in the HGPRT locus CHO gene mutation assay with and without S9. In rat liver, no damage to DNA was detected, but treatment with PolyCTFE 3.1 oil or acids caused an increase in cell division of hepatocytes, a physiological response of questionable relevance to humans. The results of the mutagenetic battery predicts no genetic risk from PolyCTFE 3.1 oil.[15,16]

The CTFE oligomeric acid formed from the tetramer caused the same toxicity as observed with PolyCTFE 3.1 oil. These data are consistent with the formation of acid metabolites as part of the mechanism of PolyCTFE 3.1 oil toxicity in rats. The comparative study of formulations also found that the tetramer was the more toxic oligomer. This comparative study demonstrates that a less toxic formulation of 3.1 oil can be blended by avoiding the tetramer. The formulation without the tetramer contained higher molecular weight oligomers that are potentially as toxic as the tetramer. The potential risk of these higher molecular weight oligomers is greatly diminished by their very low volatility and much smaller percentage of the total formulation.

The subchronic toxicity of the present operational hydraulic fluids and another candidate hydraulic fluid were determined to provide a database for comparison with PolyCTFE 3.1 oil. Without this information, it is difficult to make decisions about the relative risks of PolyCTFE oils versus existing hydraulic fluids. Subchronic (4-week repeated dosing) studies for the current hydraulic fluids and a low temperature version of MIL-H-83282 were conducted in an attempt to fill this data gap. The operational fluids, MIL-H-83282 and MIL-H-5606, and PolyCTFE are relatively nontoxic after an acute exposure. The phosphate ester hydraulic fluids possess a degree of acute toxicity. Oral dosing was used in place of inhalation studies because the time to do 90-day studies for each hydraulic fluid would be several years and the cost of a 90-day inhalation study would be much higher. The comparative study of hydraulic fluids revealed that the hydrocarbon-based fluids, MIL-H-5606, MIL-H-83282, and the low-temperature version of MIL-H-83282, cause an increase in protein in the kidneys. Protein accumulation in the kidney is a male-rat-specific effect seen after exposure to hydrocarbons such as gasoline.[26,27] This type of hydrocarbon-induced kidney lesion frequently progresses to kidney cancer in the male rat.[28] This kidney lesion of male rats is not believed to be relevant for humans.[29] In addition, the in-use hydraulic fluids, MIL-H-5606 and MIL-H-83282, increased peroxisomal beta-oxidation, an indicator for peroxisomal proliferation, the same as PolyCTFE 3.1 oil. The relevance of this finding to humans is also questionable.

Risk Assessment

The Air Force needed an interim exposure guideline for PolyCTFE 3.1 oil during the development of a new hydraulic system capatible with these oils. A guideline was proposed based on equivalence to the NOAEL in the rat of 50 mg/m^3. Using an average molecular weight for the 3.1 oil of 450 g/mole, 50 mg/m^3 equates to 2.5 ppm. Even if one assumes that the rodent response is relevant to humans, three factors

indicate that the primate (including the human) is at substantially lower relative risk:

1. Pharmacokinetic considerations; the production of the acid metabolites is less efficient in primates.
2. Elimination characteristics; the clearance of the more toxic tetrameric oligomer was found to be more efficient in primates.
3. Interspecies differences; the cellular response to the acids is markedly lower in primates.

These factors combine to produce a built-in safety factor of several orders of magnitude, mitigating the need for an additional safety factor as is common practice. Based on these considerations, an 8-hour time-weighted average (TWA) exposure limit of 2.5 ppm and prevention of liquid contact with the skin is believed to provide appropriate health protection for exposed personnel. This recommendation is a preliminary guideline, not Air Force policy. The interim guideline could be changed by new experimental data, further scientific review, or federal regulatory action.

Relationship to Other Fluids

All of the hydraulic fluids examined show some degree of toxicity in rats, and several would be likely to cause tumors in the liver or kidneys of exposed rats if a lifetime cancer study were to be performed in this species. Although the target tissue in the rodent is different for PolyCTFE-based fluids than for the hydrocarbon-based fluids, neither of the two responses, peroxisome induction or kidney toxicity, are considered to be predictive of human risk. The use of PolyCTFE-based hydraulic fluids should not cause a significantly increased hazard compared to other in-use and proposed hydraulic fluids. However, because the rodent data do at least suggest the potential for toxicity, both PolyCTFE-based and hydrocarbon-based hydraulic fluids should be handled prudently, with appropriate industrial hygiene precautions taken to minimize inhalation exposure and skin contact.

Experimental Design

A decision tree was established in order to conduct a comparative risk assessment for PolyCTFE 3.1 oil. A series of experiments were conducted based on the decision tree to answer the questions raised by the first 90-day study and to provide data necessary for establishing an interim guideline for the safe use of the 3.1 oil. This approach resulted in a risk assessment for the Air Force in a timely manner. This comparative approach demonstrates a process of conducting toxicity studies in a more efficient and structured manner than simply examining data at the end of a series of unrelated, classical toxicity studies.

Benefit

The result of conducting this risk assessment for the Air Force was the continuation of the development of the 3.1 oil for advanced aircraft. Contractors had suspended studies until the interim guideline was reported to the hydraulic fluid engineering community. In addition, there is interest by the other services in PolyCTFE hydraulic fluid for their advanced systems. The use of this class of materials is being more widely considered as lubricants, greases, and oils.

Acknowledgments

We would like to acknowledge the many researchers in our division who contributed the data necessary for this risk assessment. It was truly a team effort. In particular, we would like to thank Allen Vinegar for technical support and for permission to include part of his modeling results (Figures 5 and 6 and Table I), Ed Kinkead and Nick DelRaso (Table II) for results from a number of their studies, and Carlyle Flemming for his statistical support. We would also like to acknowlege Ed Snyder and Lois Gschwender of the Materials Directorate, Wright Laboratory for their technical assistance and support of this effort.

The animals used in this study were handled in accordance with the principles in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on Care and Uses of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council, DHHS, National Institutes of Health Publication #85-23 (1985), and the Animal Welfare Act of 1966, as amended.

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Issues in Risk Management

The Role of Human Error in the Estimation and Management of Risks

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Early risk analyses were often subject to the "hardware fallacy" — the understandable but erroneous assumption that almost all the risks in technological systems could be understood in terms of physical and biological variables. Accumulating evidence shows that this assumption was wrong. The "real risks" in most technological systems are shaped profoundly by humans as well as hardware, and system designs based on inadequate understandings of predictable human behaviors can lead to increased rather than decreased risk. Risk assessments are also produced by humans, and accumulating evidence makes it clear that the experts who calculate risks are prone to the same types of errors and biases that afflict "normal people." In addition, the real risks of technological systems include the impacts that are created for the broader society, and those impacts depend on the facts that get through to the public, not the ones that are believed in the agencies or the technical community.

Although early studies often speculated that public opposition might reflect misunderstandings or inaccurate information, those speculations have been shown by empirical research to have little factual basis. Instead, the key variable appears to involve recreancy, or the failures of specialists, experts, and technological systems to perform their tasks with the necessary vigor. Given the increasing complexity and interdependence of society, such failures by experts and institutions may have been the most significant of all factors in creating public opposition to science and technology. Expert misconduct is so corrosive for public support of science and technology that, at least for those of us who believe in the value of science, the potential for recreancy may represent the biggest risk of all.

Introduction

This paper begins with a confession and a definition. The confession is that I am a sociologist. The definition is that a sociologist is not a socialist, is not a social disease, and is not a social worker, but rather is a social scientist — someone who believes no law of nature requires us to stop using the scientific method when the analysis moves beyond the human cell and considers the whole human organism, or more broadly, when questions of human behavior become involved.

The "people side" of the risk issue will be addressed through a discussion of the ways in which risks are managed by certain groups of humans (often technical organizations and government agencies) and perceived by other groups of humans (often nearby communities and members of the general public). Both of those topics are large ones, and both have been dealt with in growing detail in the social science literature that will be cited, at least selectively, in this paper. For summary purposes, however, at least some of the central findings of this broad body of literature can be condensed into four points that will be discussed in this paper. The first is that the impacts of technological risks on society depend on the facts that actually get through to the public, not merely the ones that are believed in agencies and in the technical community. The second is that, contrary to the beliefs that were expressed in some of the earliest speculation on the topic — and often "expressed" with something akin to passion — opposition to many forms of technological development appears to be not only widespread and deeply felt but also to be focused on specific facilities/technologies and to be prudent in origin. The third and fourth points will switch the focus from "them" (the members of the general public) to "us" (the members of the technical community). Point three has to do with a special kind of wishful thinking: as technically trained people, we tend to wish we could ignore or avoid all but the factual considerations in complex decisions, but technological controversies inherently involve questions of value as well as questions of fact. The fourth and final point is that many of our discussions about risk have also suffered from the hardware fallacy — the understandable but erroneous belief that the risks of a technological system can be understood strictly in terms of physical and biological variables, when in fact, the real, "hard," quantifiable, empirical cases of technological failure often prove to depend heavily on humans and not just on hardware. The four points will be discussed in the same order as they have been listed.

Actual Impacts Depend on Facts that Get Through to the Public

In all likelihood, members of the technical community need little convincing that public views of science and technology are affected less by what goes on in the laboratories

than by what gets reported in the media; it is hard to imagine how else the information would get through to most members of the public. But are we so accurate in our usual assumptions about what gets reported? In fact, the media carry a steady diet of reports on the good news and impressive accomplishments of the scientific community, ranging from superconductivity to medical breakthroughs to improved understandings about how organizations function. When most scientists express their spontaneous impressions about media reports, however, we stress something far different. The reason is something akin to the "availability bias":[1] like members of the general public, we often have a much easier time remembering the much more dramatic news associated with technological failure, ranging from the Challenger to Chernobyl and from the Hubble space telescope to the Exxon Valdez, rather than the daily diet of good news.

One of the easiest ways to win the hearts of the technical community is through vigorous denunciations, railing at the irresponsibility of the reporters and the ignorance of the readers. Unfortunately, such an approach may win scientists' hearts, but it would have very little to do with their minds. Instead, as is often the case in the physical or biological sciences, the unfortunate truth is that the data will not necessarily validate the beginning hypothesis.

In essence, there are a few key problems with the argument, so popular at scientific conferences, that constant antiscientific reporting is being swallowed whole by a gullible public. The first is that systematic studies have found precious little evidence of an antiscience bias in any of the media outlets this side of the lunatic fringe.[2–5] The second problem is that, much to the chagrin of generations of mass communication researchers who had assumed they would earn tenure by demonstrating the effectiveness of one type of media message over another, perhaps the most common finding in the mass communication literature is in essence a nonfinding. In general, studies have found that mass media reports have precious little influence on people's actual views.[2,3,6]

If you would rather not read the substantial body of literature on this topic, you may wish instead to reflect on two pieces of information. First, if you think back on the era that has seen the greatest growth of public criticism toward science and technology, namely the past three or four decades, you will realize that much of the growth in criticism has taken place during precisely the era that has also seen unprecedented expenditures, both by government bodies and by private entities, trying to tell people just how safe and wonderful our technology has become. Remember the vast sums spent on "risk communication" messages about "My Friend, the Atom," during the 1950s and 1960s? Remember the vast mobilization that arose against nuclear power during the 1970s and 1980s? Second, more recent, systematic studies have found that opposition toward nuclear waste facilities, in particular, has increased during the very time periods when project proponents were spending large amounts of money on "public education campaigns" which were intended to have the opposite effect, namely to convince the citizens of intended host regions that the facilities would be a safe and desirable form of economic development. This is not only happening in the United States[7] but also in nations commonly seen as being more deferential toward technology, such as Japan,[8] Taiwan,[9] and in a less systematic case, Korea.[10]

Public Concerns Tend to be More Prudent Than We Once Assumed

A common complaint is that, "If only people had the facts, they'd support our technology." Conferences with slick, expensive presentations have put forth a similar point; the people who know the facts — people like us — tend to think we are great. Opposition comes either from ignorance or irrationality, since, after all, to know us is to love us.

A few of the earlier and better-known articles in the risk literature featured the same type of speculation. Unfortunately, what they appear to have been expounding is a point of view that had everything going for it but the facts. A growing body of literature has found that the opponents of technology tend to be just as well-informed as the supporters.[11–19] In several studies, in fact, researchers have even found that opponents were characterized by an active searching for information, whereas the supporters of the controversial facilities were those who, "by their own accounts, were noticeably and, in many cases, intentionally uninformed."[20]

Although it would be premature to describe the differential information-seeking as universal, it has been encountered repeatedly in the studies done to date.[21–24] One study even found that a group of citizens became amateur but reasonably skilled epidemiologists in an effort to obtain the types of answers that relevant health authorities were unable or unwilling to provide.[25] Particularly in studies of technological disasters, in fact, members of citizen groups often describe one of their greatest frustrations as being the difficulty of obtaining the credible, scientific information they actively seek.[23,26–28] In short, to the extent to which many of us have long assumed that "public ignorance" has been the factor at fault, the evidence shows we have been barking up the wrong fault tree.

How could so many smart people have been so wrong, so consistently? The problem brings to mind the definition of "expert" offered by Yale University Professor Charles Perrow: "a person who can solve a problem better or faster than others, but who runs a higher risk than others of posing the wrong problem."[29] Is it possible that we have failed to understand public concerns because we have been depending on the wrong assumptions and focusing on the wrong questions?

Figure 1 offers an illustration of the potential problem. It reflects one of the remarkable features of most discussions

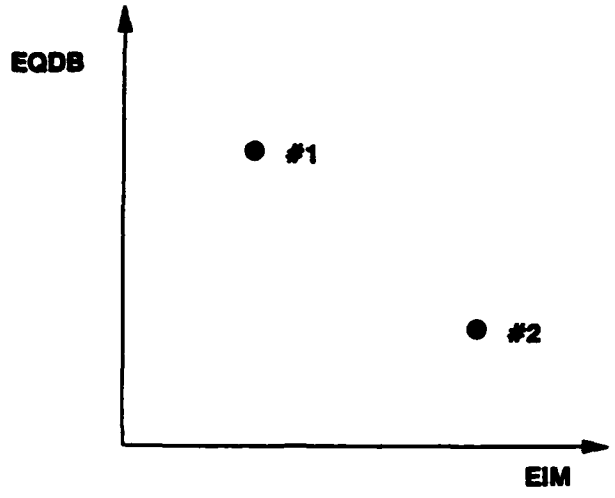

FIGURE 1. Which is the worst risk?

about risk — that almost every presentation contains a few technical-sounding acronyms that will be completely foreign to any but the chosen few. Figure 1 has a pair of acronyms that are intended to fit the very same pattern. The first acronym is EQDB, which stands for the complex, hard-to-grasp concept of the "Expected Quantity of Dead Bodies." Those of you who may not yet be among the chosen few might wish to think of this concept as being roughly analogous to the view of "risk" that has tended to be the focus of attention within the technical community to date, involving potential threats to human health. The "EIM" on the other dimension will not be defined until later, because the point of Figure 1 is to ask a question.

All of us have heard the speeches and read the articles about putting risks "into perspective," often involving arguments that the public is crazy to be worried about technology X, when after all, the "real risks" of X are far lower than the risks of alternative activities such as smoking (for almost any technology) or perhaps even lower than the risks of eating peanut butter and drinking a diet soda (for the more flamboyant). Such arguments, of course, make good "sound bytes," and they would even make good sense if, in fact, EQDB were the only concern. But is it possible that there are other factors involved, potentially even including "EIM," such that people might reasonably be worrying about something that, sad to say, we "experts" might have overlooked? While you are pondering that question, incidentally, you may wish to consider the fact that at least one member of the risk assessment community has finally been able to state succinctly the meaning of life — life is a sexually transmitted condition with 100% mortality.[30] You may also wish to ask yourself if there really is such a thing as "a fate worse than death."

While you are carefully considering these questions, it needs to be noted that, due in part to the successes of science and technology, we have made substantial strides in at least reducing the annual rate of that age-old adversary, EQDB. Figure 2 provides a simple summary of the relevant data, which are straightforward extrapolations from life expectancy figures for the United States. The figure shows that traditional risks, or the risks of death, have dropped dramatically over the past 150 years, such that the average U.S. citizen today has an implied annual risk of death roughly half as high as that of the average citizen of 150 years ago, even after excluding the effects of literal slave labor.

Once again, if my purpose were to pander to preexisting predilections, I could stop here and "pound the podium" about how Figure 2 offers proof of the value of science and technology, about the ingratitude of the general public toward all that our scientific forbearers have already done, and about the ignorance of all of those who oppose what we want to do next.

Such an approach, unfortunately, would have a few problems. First, if you think back to the last time when someone started a conversation by calling you an ignorant ingrate, you will probably recall that this approach did little to increase your receptivity toward that person's message. The second involves the fact that we are discussing life expectancy. As the term itself implies, the current life expectancy is more or less what all of us feel, with reason, that we have a right to "expect." Not even members of the scientific and technical community would be likely to respond with favor to the argument that because our great-great-great-grandparents only lived about 35 to 40 years, on average, what was good enough for them should be good enough for us. The third problem is that, as will be noted below, while the EQDB has been going down, something else may have been going up.

Fourth and finally, although such "podium pounding" may be understandable or even cathartic, it reflects a thorough misunderstanding of what it means to say that we live in a society that is technologically advanced. One of the usual assumptions is that technological advances will mean that we "know more" than did our great-great-grandparents; collectively, of course, that is true. But individually, we actually know far less about the tools and technologies on which we depend — a point made initially by one of the earliest and most articulate proponents of "intellectualized rationality," Max Weber, roughly three-quarters of a century ago.[31]

In the early 1800s, approximately 80% of the American population lived on farms, and for the most part, those farm residents were capable of repairing or even of building from scratch virtually all of the tools and technologies upon which they depended. By contrast, today's world is so specialized that even a Nobel laureate is likely to have little more than a rudimentary understanding of the tools and technologies that surround us all, from airliners to ignition systems to computers to copy machines. Far more than was the case for our great-great-grandparents, in short, we literally "depend on" the technology to work properly, which means that we depend on the system as a whole — meaning, in turn, that we have

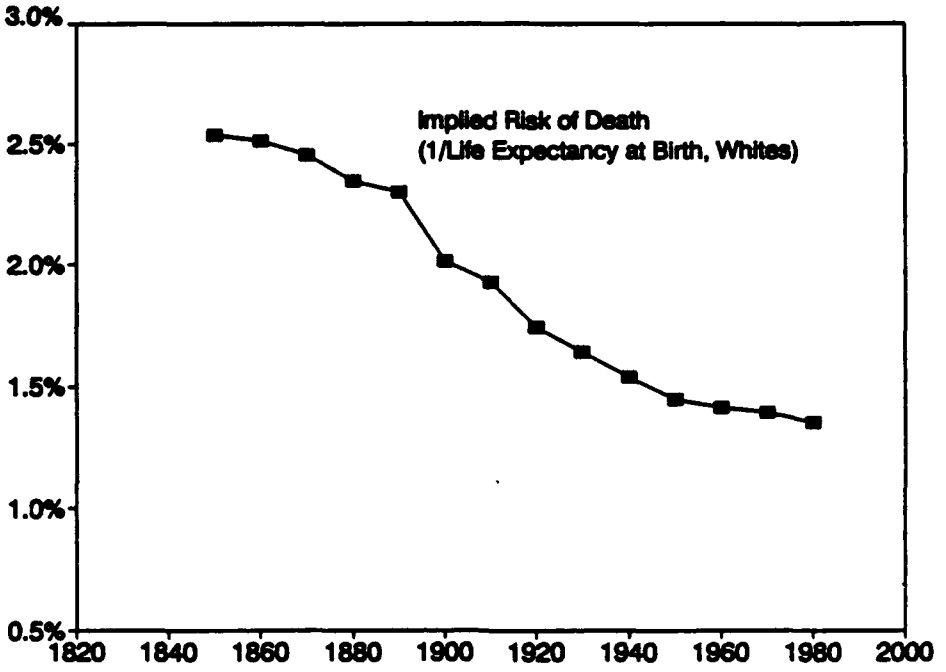

FIGURE 2. The long-term decline in the risk of death in the United States. Data sources: *Historical Statistics of the United Sates, Historial Times to 1970* (U.S. Bureau of the Census, 1975) and *Statistical Abstracts of the U.S.* National figures are available only as far back as 1900. Data for 1850–1900 are drawn from Massachusetts, where 99% of the enumerated population at the time was white. The 1870 figure is an interpolation.

become dependent on whole armies of specialists, most of whom we will never meet, let alone control. As economists are fond of pointing out, there is no such thing as a free lunch. The achievements of science and technology have been important and even impressive, and they have helped to bring about a level of physical safety and material wealth that is simply unprecedented. However, they have done so at a cost — a cost of increased interdependence.[32]

This point is summarized in Figure 3, which illustrates the technological risk crossover. Using a very simple index of interdependence, based largely on the proportion of the citizenry not involved in growing their own food, this figure shows that, during the very era when society has been enjoying a substantial decline in traditional risks — EQDB, or the risks of death — there has been a substantial increase in the risks related to interdependence. The most serious of these risks, if you will pardon a technical term that is meant to be taken seriously, involves recreancy — in essence, the likelihood that an expert or specialist will fail to do the job that is required.[32]

Recreancy is derived from the Latin roots *re-* (back) and *credere* (to entrust), and the technical use of the term is analogous to one of its two dictionary meanings, involving a retrogression or failure to follow through on a duty or a trust. The term is unfamiliar to most, but it is necessary because of the need to refer to behaviors of institutions or organizations as well as of individuals and, importantly, because of the need for a word that is factual, not emotional, in its meaning. Indeed, it may tell us something that over time virtually all of the common words with comparable meanings have come to take on a heavily negative set of value connotations. To say that someone is responsible, competent, or trustworthy, for example, is to offer at least a mild compliment, but to accuse someone of being irresponsible, incompetent, or of having shown a "betrayal" of trust, is to make a very serious charge, indeed. While "recreancy" may not be an everyday term, however, we need such a word precisely because of the need to avoid the emotional and/or legal connotations of the available alternatives. Often, even when the relevant failures are severe in their consequences, they result not from evil intent so much as from a failure of foresight. At least in retrospect, these mistakes are often easy to understand, particularly for people who are familiar with the technological system in question. In essence, the source of "fault" can be as likely to lie as much in the situations as in the intentions, and as much with organizations as with individuals.[32,33] Finally, for those who have not already figured out the connection, incidentally, recreancy can also be seen as the one-word equivalent of the second acronym in Figure 1 — "EIM," or "Evidence of Institutional Mess-Up."

Technological Controversies Inherently Involve More Than Just "Facts"

Although it is understandable that people who are most comfortable in the realm of facts want to "reduce" technologi-

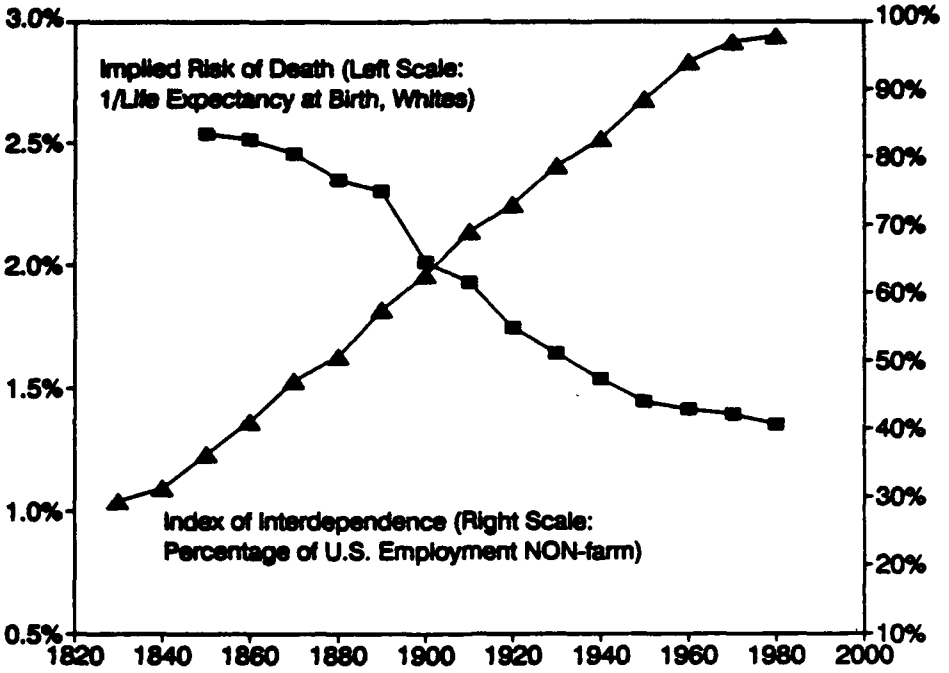

FIGURE 3. The technological risk crossover in the United States. Data sources: *Historical Statistics of the United States, Historical Times to 1970* (U.S. Bureau of the Census, 1975) and *Statistical Abstracts of the U.S.* National figures on life expectancy are available only as far back as 1900. The data for 1850–1900 are drawn from Massachusetts, where 99% of the enumerated population at the time was white. The 1870 figure for risk of death is an interpolation.

cal conflicts to being simply "factual disagreements," any number of authors have now shown that such hopes are no more realistic than the alchemists' ancient dream of being able to turn lead into gold.[19,34–40] The world simply does not work that way.

Instead, in risk-related controversies, often the greatest simplification we can hope for is to be able to reduce a debate to a pair of questions: one is potentially scientific and factual and the other is not. The factual or scientific aspects of the debate can be reduced to a single question: "How safe is it?" The value-based or nonscientific problem poses a different question: "Is that safe enough?" As would be emphasized by any risk assessor who cares about his or her scientific credibility, even what I am calling the "scientific" question here often will come down to what Alvin Weinberg called a "trans-scientific" question (i.e., one that can be asked in scientific terminology and may seem answerable in principle, but one that will often prove in practice to be effectively unanswerable during the time we most want or need an answer).[40] Will a planned nuclear waste repository be able to keep nuclear wastes away from the environment for 10,000 years, for example? We may certainly need to hope so, but the only way to answer the question with what we would normally see as scientific certainty would be to build such a facility and then wait a few centuries. A truly "scientific answer" may ultimately become available but may do so too late to provide a useful source of information for policy debates of the 1990s.

Yet, when attention turns to the second question — how safe is safe enough? — the limitations of scientific expertise become far more obvious. Although scientists are as capable of offering answers to this question as are any other citizens, our answers are neither more valid nor "more scientific" by virtue of having been offered by scientists. There simply is no such thing as a "scientific" way to compare apples against oranges against orangutans. Instead, at least in a democracy, when it comes to value-based questions (e.g., how safe is safe enough?) another word for "scientist" is "voter."

Although it may make a great deal of sense for narrow, technical questions to be delegated to narrow, technical experts, one of the fundamental principles of a democracy is that the broader, guiding decisions should reflect "the will of the governed." As Perrow's definition of "expert" would suggest, moreover, scientists' answers to these value-based questions often differ markedly from the will of (the rest of) the governed — often by placing more emphasis on cost-containment and efficiency while placing less emphasis on long-term safety.[39,41–43] So long as we are, in fact, just implementing decisions that do adequately reflect the will of the governed, our emphasis on efficiency can be a very good thing, but if we are being asked, in effect, to be making decisions, for example, on "how fair is safe enough?"[32] we are stepping into a role for which we are clearly the wrong people. It may be for a reason that we want efficiency from our mechanics

Fact 1: The Three Stages of Awareness
(from O.D. Duncan, 1978)

Stage 1: Technical Question
("Will it work?)

Stage 2: Economic Question
("Will it work economically?")

Stage 3: Sociopolitical Question
("What will the technology do to society,
and what will society do to the technology?)

Fact 2: The Law of Probable Dispersion

Whatever hits the fan will not be evenly distributed.

(also known as the "How Come It All Landed on Me?" Law)

Fact 3: The Paradox of Bucks and Blame

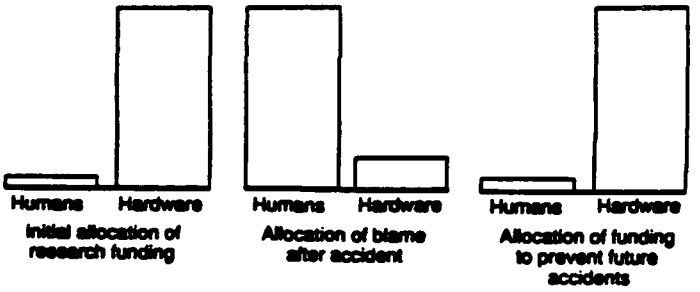

FIGURE 4. Freudenburg's facts about technological fiascoes.

but justice from our judges.

Real Risks Tend to Depend Heavily on Humans as well as Hardware

All of this brings us back to the hardware fallacy — the implicit belief that it is possible to predict "the real risk" of a technological system simply based on physical and biological variables. Many of my scientific colleagues are surprised when they first hear this belief characterized as a "fallacy." After all, these are "technological" systems, aren't they? We do, in fact, use that terminology, but technological systems include "techniques," "technicians," and "technology." In fact, when was the last time you heard of a major technological disaster being blamed on anything other than "human error?" There are a few isolated examples, but for virtually *all of the fiascoes* that have become household terms — Challenger, Chernobyl, Bhopal, Exxon Valdez, or even the Hubble space telescope — one of the commonalities is that blame comes eventually to be pinned on the vague and sometimes politically expedient category of "human error."

So pervasive is this tendency that, in response to charges from my biological and physical science colleagues that social scientists never come up with general "laws" or principles, I have produced what I immodestly call "Freudenburg's Facts about Technological Fiascoes" (Figure 4). The immodesty, however, comes not so much from calling these observations "facts" as in taking credit for them; at least the first two of the three have already been identified by someone else, and I frankly would not be surprised if even the third of them were not also to have been said elsewhere before.

Fact #1 has been adapted relatively freely from Duncan.[44] My version holds that, at least for the technological controversies that have erupted into public awareness, the social, political, cultural, and "value" questions have received attention only late in the game. Initially, when the only people paying attention to (what will eventually become) a technol-

ogy are scientists and engineers, attention tends to be focused only on what I call the Stage 1 question — can this idea be made to work? Often, the answer is "no," but for a subset of the cases where the answer is "yes," attention next comes to focus on the Stage 2 question — can it be made to work profitably? Here again, often the answer is "no," and the idea is soon forgotten. For a subset of the potential technologies, however, attention soon comes to focus on the Stage 3 question — can it be made to work in a way that will fit in with the rest of society in a way that is reasonably appropriate? Although the implications for domestic tranquility are unfortunate, often the fact is that this third question is recognized as a question only when at least the initial answer appears to be "no." Equally sad, in many such cases, if only the question had been recognized and addressed at an earlier stage, it might have been possible to develop the technology in a different way, creating fewer disruptions both for the developer of the technology and for society more generally.

Fact #2 tends to be both a reason for the recognition of the sociopolitical questions and a reason for the responses that follow. It involves the "law of probable dispersion," which I first saw on the wall of a graduate student office at the University of Wyoming in 1975. Given its almost universal applicability, various versions of this principle have been published in a number of "Murphy's Law" compilations, and failures to take the law into account have made a mockery of any number of contingency plans. In an analysis of the response to the Exxon Valdez, for example, Clarke found that, although several of the five contingency plans for spill responses could be said, charitably, to have anticipated a spill of such a magnitude, none of them could be said to have anticipated the ineffectiveness of the response.[45] One of the key reasons is that all of the plans effectively ignored the fact that real-world organizations tend to be at least vaguely aware of the law of probable dispersion, and accordingly, much of the early response to the spill was characterized more by the effort to pin the blame on other organizations than to work with them.

Fact #3 is a distillation of my personal observations of essentially all of the technological fiascoes I have been following, at least in the United States. In most such cases, three stages can be readily identified. In stage 1, before the accident, a great deal of funding may be devoted to research in a variety of disciplines, but almost none of that funding will be invested in systematic analyses of human and organizational behaviors. Usually, the range will be between 0% and 3%, and I have yet to encounter a case where the investment has been as much as 5% of the total research budget. Stage 2 involves the investigations that are carried out after the accidents, during which some 80% to 90% of the blame will be attributed to humans, not hardware. In Stage 3, of course, because we are rational scientists who learn from our mistakes and because we want to make sure our risk-management investments are proportional to the real sources of risk involved, we devote from 0% to 3% of our research budget to human and organizational factors that account for 80% to 90% of the risk.

Conclusion

Perhaps the simplest way to summarize is to note that scientists and the general public tend to have dramatically different levels of faith in technology — and in those who manage it — with the realization that "faith" is, in fact, the correct word for describing the orientations of scientists, as well as those of the general public.[34,39,46,47] As responsible scientists are often among the first to point out, those of us in the scientific community are neither omniscient nor infallible. Even spending a lifetime in studying natural laws may not allow an individual to repeal any of those natural laws — and that may include Murphy's Law.

Anyone who has spent a significant amount of time in science knows that errors and missed guesses are common, not rare. Experiments fail to work properly, cherished hypotheses are demolished by the data, papers take three times as long to write as had been expected, and the phone always rings at the wrong time. Although both the scientist and the common citizen have some recognition of this fact, however, the two are likely to differ substantially in interpreting its implications. To the scientist, such errors and problems tend to be altogether unremarkable; the point is simply to learn from one's mistakes, and indeed, a popular book has recently examined "the role of failure in successful design."[48]

The problem arises when we move from the laboratory to the real world and when the scientist's mistake is not just a source of new information but also a source of new and tangible consequences. The problem, in short, arises from the possibility that the scientist or the agency will make the mistake, but the citizen will be forced to live with the consequences, particularly in cases where there is a chance for those consequences to be severe.

Today's citizen has learned for good reason to suspect that things may not work as advertised. The world is full of con artists, stereotypical used car salesmen, and others who have something to gain from promising more than they can deliver. Given the realities of an increasingly complex and interdependent world, it is not the least bit unreasonable for a citizen to ask what danger might be caused if a specialist fails to fulfill a promise. From this perspective, in fact, what may be unreasonable is the way in which those citizen responses have been interpreted by the scientific community.

The sad fact is that those of us who make up the scientific community have spent many years dealing with public concerns in a decidedly unscientific way. The public has been both denounced and "educated," but rarely studied, listened to, or understood. The net result is that public opposition has grown to levels that are virtually unprecedented, and the rate

of progress toward dealing with many forms of technological controversy has grown asymptotically closer to zero.

The scientific way to approach public perceptions, by contrast, is neither to damn nor to dismiss them, but to seek to analyze and understand and then to deal with them. When we take this more scientific approach, moreover, we can begin to understand why past approaches have been so overwhelmingly unproductive. If public opposition has grown despite our concerted efforts at "public education," perhaps it is because the public is learning different lessons. At least some of the lessons involve the potential for recreancy, stemming not just from spectacular accidents, such as the one at Chernobyl, but also from less dramatic incidents at Rocky Flats, Fernald, Hanford, and other sites, particularly those sites where management problems turn out to have been more serious in retrospect than was stated or perhaps even recognized at the time.[43]

Perhaps all is not lost, however, if we can begin to educate ourselves. Rather than becoming defensive when the public complains about the potential for mismanagement, we need to do more to deal with the nonzero possibility that something unexpected may, in fact, go wrong. The quantitative data[32] make it clear that recreancy concerns are so corrosive to public support of science and technology that, for those of us who make up the scientific and technical community, it may be that nothing will prove more threatening than further examples of our own failings. For those of us who are committed to the maintenance and strengthening of our nation's scientific and technical capacity, the potential for recreancy may present the greatest risk of all.

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Participation in Risk Assessment and Management

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The following is the abstract of the presentation by Ms. Lynn. Her paper is not available for publication at this time.

Technical expertise and empirical scientific validity have not proven to be a sufficient basis on which to make decisions about the conduct of technological development in the United States. This is partly because our conception of the nature of science and engineering that undergirds regulatory initiatives and technological proposals has changed. From an initial definition which stressed probabilistic, if not objective science, we moved to an understanding of the role that values play in the models and assumptions that scientists and engineers choose. However, this new understanding still kept the public debate focused on scientific and technical issues. Increasingly, citizens are insisting that nontechncial, societal, and cultural values be included in policy deliberations. New forms of dialogue, collaboration and cooperation among citizens, scientists, and policy makers exist that make risk assessment and management decisions less contentious and more reflective of the American democratic system.

Ethics and Risk Management

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For more than a decade, some of us have been involved in discussions and arguments about the ethics of risk management. Part of that debate has been about the methods and applications of prescriptive analysis in making decisions involving public risk. By "prescriptive analysis," I mean any systematic approach — it need not be quantitative — to assist risk managers in making decisions consistent with their value judgments and their information about a problem. No one could seriously object to prescriptive analysis *per se*, but of course, analysts must use some particular method, and different methods can raise different objections.

In the early days, the ethical debate focused on cost–benefit methods for assessing risks and comparing them to other values. Cost–benefit analysis is subject to a number of serious objections, which will be very briefly described in this paper.

Introduction

Cost–benefit analysis has a conception of value and a decision rule. The classic cost–benefit conception of value is "revealed preference theory," which holds that the starting point for identifying values in a prescriptive analysis is an individual's preference for something, interpreted and measured as a willingness to pay for that thing. Revealed preference theory tells us to look at real economic data, but if these behaviorist strictures seem excessively rigid, we can modify the evidential requirements to include contingent valuation methods or expressed preference theory.

The cost–benefit conception of value is also individualistic. All values are monetized as individual willingness to pay. The cost–benefit decision rule says that after all risks, values, and preferences for each individual have been assigned monetary values, they should be added together and the alternative chosen that maximizes net benefits (or an alternative chosen if benefits outweigh costs).

Discussion

Cost–benefit analysis has been criticized both for its conception of value and for its decision rule. In turn, the conception of value has been criticized, both for its monetary standard and for its methodological individualism. Thus, we have three kinds of criticisms to consider:

1. Those directed at the behavioral and monetary standards of value embodied in revealed preference theory.
2. Those directed at the methodological individualisms.
3. Those directed at the decision rule.

Objections to the behavioral and monetary standard suggest that cost–benefit methods cannot account properly for special or sacred values, or for moral conflict. The most publicized criticism of cost–benefit analysis is that it puts a dollar value on human life and health or on protecting the environment. It invites us to regard these things as commodities and to show a willingness to trade them for other "consumer" goods, a willingness that many would take, in itself, as a sign of moral corruption. Of course, the defenders of cost–benefit methods argue that deciding what to pay is what risk management is all about; therefore, the only issue is whether we are going to be honest and explicit about it.

The debate has not, in my opinion, been resolved, but this objection suggests another and deeper criticism of the behavioral and monetary metric of value, that it will surely lead to moral distortions. Some of our more cherished values may be tarnished or cheapened by our showing a willingness to pay for them. Take sex, for example; it is an important value for which many people sacrifice greatly, but it is not uncommon for these same people to be unwilling to pay for it. Our consumer behavior does not always reveal our most sincere and reflective thoughts about what is most important; nor can it show the difference between being indifferent, because the alternatives seem to us pretty much equal in value, and being conflicted or unable to choose, perhaps because we find the alternatives incomparable on a single scale of value.

We also live in a world of other actors and choosers, whose behavior affects our outcomes. Our rational choices, both in the economic and in the political sphere, will often be strategic. I act in part on the basis of my beliefs about how my behavior will influence the beliefs and behavior of others, about how my behavior will influence another's beliefs about my beliefs about his/her behavior, and so on. We simply cannot infer preferences or values directly from observing a rational person's choice behavior.

Criticisms of the methodological individualism of cost–benefit analysis call attention to concerns about distributive justice. Simply aggregating risks, costs, and benefits will lead to decisions that will especially disadvantage the poor, rural populations, and (because of the discount rate applied to all

monetized values) future generations. Of course, adjustments can be made to the preference theory to counter these implications, but unless they are made simply to correct for "income effects," they are either *ad hoc* modifications or else they lead in the direction of another method of prescriptive analysis, decision analysis, which I shall discuss presently.

Consider an example that illustrates both the objection about distributive justice and the problem with the cost–benefit decision rule. Suppose we have a given amount of resources and must choose to spend the entire amount on one of two alternative projects. One project would reduce, by a given amount, the average individual risk of premature death and would save, let us say, ten lives over a given period of time. The second project would reduce, by a greater amount, the average individual risk of premature death in a sparsely populated rural area but would save only five lives over the same period . Assuming all other factors are equal, the cost–benefit decision rule would tell us simply to reduce the risk of the urban population.

Now, I do not mean to suggest that this decision is clearly the morally incorrect one or that our intuitions about distributive justice dictate that we must do otherwise. Indeed, in cases like these, I think it is very difficult to know what to do. The objection to the cost–benefit decision rule is that it short–circuits the dilemma. Government agencies that have suggested using a cost–benefit decision rule have been criticized or sued for abandoning their legislative or political mandate and for approaching the special values they were created to protect with the cold and detached eye of an accountant looking only for the biggest "bang for the buck." Distributive justice does not carry much weight in analyses.

This criticism may also point to the special nature or sacredness of certain values, which may call for certain symbolic measures. In any case, it suggests the importance of procedural values to which cost–benefit methods are entirely blind. In the example of the choice between urban and rural risk reduction, perhaps the concerns about distributive justice are best met by adopting a procedure for making the choice that represents the concerns of both sides fairly. Ensuring that decision rules reflect different procedural values is surely of primary importance in resolving many risk disputes.

Thus, there are three kinds of ethical objections to cost–benefit methods. The behavioral and monetary conception of value introduces moral distortions and fails to reflect special and sacred values. The methodological individualism leads to decisions that ignore our concerns for distributive justice, and the decision rule is incompatible with procedural values.

In the discussion of the ethics of risk management, however, cost–benefit analysis is a thing of the past. Recently, the discussion has shifted to decision analysis, in large part because decision analysis can avoid the criticisms just described. Decision analysis makes a minimum commitment to any conception of value. It is thus flexible in determining how alternatives are weighed and compared. The decision rule is not an algorithm but a prescription. We can reject it, and decision analysis can even prescribe against its own use in a given situation.

Decision analysis is supposed to be a formalization of common sense, to be applied especially to problems that are too complex to rely on common sense alone to analyze adequately. It is based on the axioms of utility theory, which can be interpreted merely as defining a coherent and consistent set of preferences. We can fill in the values however we determine we should, and we can reflect uncertainties to any degree of accuracy.

I do not mean to suggest that decision analysis as a method is completely immune to ethical doubts; however, I do think the criticisms that can be raised are rather *recherché* and abstract. Moral problems can certainly arise in any *application* of decision analysis, as its proponents have been quick to recognize and admit, but I think we must agree with Ron Howard that as a method, decision analysis is basically "amoral, like arithmetic,"[1] or with Ralph Keeney that decision analysis can be made "consistent with any of the major ethic theories."[2] To see that this is true, consider how the proponent of decision analysis would respond to the three kinds of objections I raised against cost–benefit analysis.

Because decision analysis is silent about how we value a state of affairs, we are free to include special values, sacred values, nonmarketable values, and so on. The only thing we are required to do is compare and rank different alternatives consistently. That can be done without prejudice to the nature of our concerns. Even if we take some values as absolute, unable to be traded off without being compromised, decision analysis can reflect such rankings too. Decision analysis may show us how difficult it is in practice to regard some values in this way and to remain constant; however, the analysis can do this with a certain "lightness of step" without being condescending, nagging, or simply obtuse.

The minimal substantive moral commitment of decision analysis also means that it is not committed, as is cost–benefit analysis, to methodological individualism. If a state of affairs includes nonreducibly social values, these can be included. If we value certain moral rights, for whatever reason, then they contribute value to the state of affairs in which they are recognized and protected. If we value fair distributions, then we can likewise include distributions of risks, costs, and benefits among the attributes that add value to a state of affairs. We can do this either through weighing the outcomes to some individuals or groups more heavily than to others and then aggregating them, or we can do this by measuring the fairness or unfairness of the distribution of risks or consequences in a state of affairs directly and including fair distribution itself as an attribute of utility.

Finally, decision analysis allows us to count a state of affairs better in which a decision is reached by using a favored procedure rather than a state of affairs in which otherwise identical consequences are realized in a different manner.

Thus, if we must choose between saving the lives of ten urbanites or the lives of five ruralites, we could decide that the best outcome of all is to invoke a fair procedure that determines that we shall save the ten lives. We can then decide whether the outcome of invoking the procedure and saving five lives is ethically better than saving ten lives without invoking the procedure. Which outcome we value more will depend ultimately on what we think about the importance of invoking the procedures as compared with the importance of risking the loss of the five extra lives, but decision analysis will allow us to go either way on this choice.

The more one comes to appreciate the flexibility of decision analysis, the more convincing is the argument that it is indeed substantially ethically neutral. However, another conclusion to draw from these arguments, as the example about procedural values demonstrates clearly, is that decision analysis does not help us at all in resolving ethical conflicts or making moral progress in risk management because it gives us no moral guidance. The only value it promotes is consistency, respect for which may well constitute progress over our normal practices but hardly scratches the surface of our ethical concerns. Once we become convinced that methods of prescriptive analysis need not be ethically suspect, the moral debate has been neither concluded nor even advanced. Everything remains to be done, and what remains is a lot.

Conclusion

Let us look one final time at the three kinds of objections to cost–benefit analysis. The first, you will recall, was the behaviorist and monetary conception of value, which turns out to be morally distorting because it is insensitive to a range of special and important values. Decision analysis allows us to be sensitive to these values, but it does not tell us how to be sensitive to them, and that is our problem. What are we to make of values that seem compromised when we are asked to determine their economic worth? We know that people feel this way about a number of the things that are important subjects for risk management. Our surveys on risk attitudes tell us this, and the few anthropological studies in this area may help to explain them and their role in the fabric we call culture. However, we still do not know how risk managers should tiptoe around these issues, or what role a government agency may be expected to fill in giving these values the symbolic or expressive actions they demand; and lives, as well as serious economic consequences, are at stake.

Similarly, even if one method of prescriptive analysis fails to reflect the concerns of distributive justice and another one does not essentially fail in this regard, we still need to know more about the values of justice relevant to risk management. In particular, there are two issues we need to better understand. The first is the connection between fairness and procedures. If we invoke fair procedures, or even if we distribute risks equally, to what extent does this relieve us from having to be concerned with unequal outcomes? When are *those* outcomes unfair or unjust? This question points to the role of compensation, which suggests a second central question about justice. Part of understanding the special nature of certain values or the qualitative differences among values is understanding the limits of the ability compensation to achieve justice. Compensation can fail in two different ways for different reasons, either because a benefit fails to equal in amount the loss for which it is meant to compensate or because it fails to *offset* the loss because it is a failure in the kind of benefit required. When we say that a loss cannot be compensated, we can mean either that it is too great to be offset or that it cannot be offset by the nature of the value. The importance of understanding this difference will be to understand when risks can be imposed, if the losses are compensated, and when risk-imposing activities should be prohibited morally.

Finally, we again see similar issues arising when we look for morally adequate decision-making procedures. In risk management, these will often involve a requirement to involve affected parties in the decision-making process, to secure their free and informed consent. Again, the kind of risk research we have from the social sciences does more to underscore the problems than to suggest solutions. Here we have to confront the limitations in human judgment, our tendency toward preference reversals (which raises deep problems about the coherence of our values), and the difficulties of finding effective and nonbiasing ways to communicate technical and expert information.

What are we to make of all these problems? I do not know, and I do not think anyone else knows very well either. I would like to see some progress made on the ethical issues in risk management, and perhaps we shall when we can put aside our doubts about prescriptive analysis *per se*. I would like to contribute to this progress in our moral understanding; however, we all need to provide more support than this subject has received.

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Regulatory Decisions and Risk Management

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The processes of risk assessment and risk management have been subjects of ever-increasing study in recent years. Stemming from their application to engineering and nuclear safety, these techniques have been extended, particularly in North America, to include the potential health risks from chemicals. The results have been important in terms of public policy, as we wean the public from a belief in absolute safety to an understanding of the probability of risk. The concept of acceptable risk gained modern currency from the seminal paper of Chauncey Starr[1] and Lowrance's[2] thoughtful book. The distinction is, of course, between what is acceptable by whosoever makes the assessment and what is accepted by those who live with the risk. More appropriately, we should say "tolerable" rather than "acceptable," for that is indeed what we are prepared to live with for a defined period.

These studies gave a measurement to all those well-known impulses whereby individuals subject themselves to the hazards of skiing, alcohol, or motor bikes but react negatively to fluoridation, food additives, or pesticide residues, all of which are regarded with suspicion because they are imposed from outside. The acceptance of a risk depends not only on the ascribed level of risk but also on our perception and degree of understanding of that risk. Public perception of risk is often markedly at variance with the estimates given by professional scientists. We are only beginning to explore the reasons for these fears and concerns. Sometimes the gap can be overcome by education, but more often, it represents deeper, more firmly held beliefs. Psychologists have shown how important in risk perception are such factors as unknown global, catastrophic, increasing, uncontrollable, and fearsome risks.[3] This research has been used to explain and forecast acceptance and opposition to specific technologies, particularly the nuclear industry. In the final analysis, public acceptance of a risk depends on public confidence in its effective management,[4] whereas tolerance of certain risks can be linked to an expectation that alternatives will be developed, that further controls will be established, or that a specific use will be discontinued.

Introduction

Management Strategies

Regulatory agencies are required to advise on the translation of the scientific estimation of risk to the appropriate risk management option. In the final analysis, risk management decisions are political because they must respect social, cultural, and economic realities. The options available to governments to manage the risks from chemicals may, for simplicity, be considered under three headings: educational, economic, and regulatory. Each one may, of course, be applied in conjunction with the others. The regulatory option — the one most immediately associated with government action — should be considered as encompassing the range from promulgated acts to recommended guidelines and codes of practice.

The educational approach can serve to make producers, workers, and the general public aware of the risks from chemicals so that they can voluntarily take the requisite action to reduce or avoid the risk. Public information programs can enhance health promotion by advocating such sensible lifestyles as avoiding smoking, taking alcohol in moderation, and exercising regularly. Governments can strengthen the impact of these programs through advertising in the media to susceptible groups (e.g., the young) and by the personal example of community leaders. Workers can be educated in the hazards of chemicals by courses, lectures, posters, films, and by explicit labeling of chemical products. Through government agencies and supported product testing studies, consumers can be made aware of the need to use household chemicals, cosmetics, pesticides, and fertilizers with care and attention. Positive reinforcement, by publicity, can be given to those manufacturers and producers of chemical products that show corporate responsibility to their workers and the public in their treatment of chemicals, both within and outside their plants.

Economic options can provide both positive and negative incentives to the effective control of hazardous chemicals. The "polluter pays" is a principle espoused by the Organization for Economic Cooperation and Development[5] with the intention of maintaining equitable trading practices by encouraging polluters to reduce emissions. In general, the use of effluent charges will encourage polluters to reduce emissions until the marginal cost of further abatement exceeds the charge itself.[6]

Other economic instruments include pollution-control delay penalties, market emission permits, and subsidies.[7] In the first case, schedules are established in which the maximum allowable emissions are decreased over time. Market emission permits may be issued specifying maximum cumulative and dispersive emission levels for particular pollutants. Subsidies such as grants for pollution abatement

equipment may be used as a monetary incentive for pollution control. Tax deductions, rebates, and credits all play a part in the total fiscal policy of governments' economic control of chemicals.[8]

Regulatory options rely on government authority to enforce compliance with specific health and safety requirements. The authority can be through the force of law and prosecution or through the more gentle route of persuasion and recommendations. In principle, the essential elements for a health protection control program follow this pathway:

Investigation/Research →Criteria→Standards →
Regulations →Enforcement and Compliance →

That is to say, investigation and research lead to an evaluation of the health hazards, formulated as criteria. From these criteria, health standards are derived which we, in turn, convert to a legislative reality when promulgated as regulations. The final stage is the enforcement of these regulations, so that if they are not achieving the original intention, the cycle of investigations to regulation will be repeated once more. Ideally, such measures relate achievements to needs.[9]

Regulatory agencies, which control noxious agents, need a solid number to give credibility to a regulation, standard, guideline, or even a recommendation.[10] Whatever the strength of the regulatory action, a number can be a concentration (e.g., milligrams per liter [mg/L], micrograms per cubic meter [$\mu g/m^3$]), a ratio (e.g., parts per million [ppm]), an emission or discharge rate (e.g., kilograms per day [kg/day]), or a deposition application rate (e.g., kilograms per hectare [kg/ha]). Essentially, the number enables us to make a judgement as to what is safe — or, more properly, an acceptable, tolerable risk — as opposed to what is negligent or criminal.

The number should be enforceable and be amenable to change as new knowledge develops and as social values change. At best, it will be an approximation without giving an absolute guarantee of freedom of risk.

Guidelines, although expressed in the same way as standards, are envisaged more as recommendations that do not allow legal recourse to ensure compliance. They are particularly valuable in ensuring uniform environmental quality where the responsibility for public health protection is shared with other jurisdictions. Guidelines are also developed by, and appropriated to, international agencies such as those of the United Nations. In addition, guidelines are flexible, without enforcement costs, and serve as an incentive to industry. However, they have limited power (other than public persuasion), can be disregarded, and are capable of misinterpretation.

The Canadian approach to risk management derives from the appropriate legislative authority — both federal and provincial. In general, the Canadian political system has adopted a liberal democratic view of the state. It accords to market forces the primary initiatives in the introduction of new products and goods — and, hence, of new hazards. The state does, of course, referee the process and, on occasion, assumes direct involvement through public enterprise. Control of toxic substances can be applied from manufacture to disposal. Federal jurisdiction, particularly the criminal law, trade, and commerce powers, provides the basis for the major acts designed to protect the health of Canadians from environmental hazards.[11] In all, for toxic substances, there are some 27 federal statutes that exercise some form of control, and the 10 provinces have enacted some 100 pieces of legislation.

In general, the choice of measures and strategies for regulation depend on the existing legal and social constraints of the country. Some countries, such as the United Kingdom, make use of self-regulation while others, such as the United States, adopt a more rigorous approach with reliance on the courts.[12] The Canadian approach represents an intermediate position and can serve to illustrate the general principles of managing toxic chemicals.

Scientific Estimation of Risk

A numerate society such as ours regulates by numbers. For chemical risks, these numbers are derived from epidemiology, particularly for occupational health analysis where workers have tragically been exposed to such chemicals as vinyl chloride, asbestos, lead, or arsenic; from animal tests on mammalian species; and from *in vitro* analysis, particularly for genotoxicity. In recent years, the use of biostatistics to provide quantitative risk assessments for carcinogenesis has led to the use of calculated numbers to develop policy decisions on the regulatory control of chemicals. This approach has been particularly favored by the U.S. Environmental Protection Agency (EPA). It is usually acknowledged that a lifetime risk of 10^{-6} is so low as to be generally acceptable. Nearly all regulatory decisions on chemical carcinogens involve higher levels of risk. In Canada, for example, the lifetime risk of being killed by lightning is 1.4×10^{-5}.[13]

The application of guidelines for risk for animal carcinogens in drinking water in Canada has been given, at their maximum recommended concentrations, as annual risks of cancer of 2×10^{-7} for nitrilotriacetic acid (NTA), 5×10^{-7} for trihalomethanes, and 2×10^{-8} for alachlor; at 100 ppb formaldehyde in indoor air, the annual risk of cancer is 7×10^{-7}.[14] These are very low annual risks — much lower than that for radon in indoor air at 800 Bq/m^3 which translates into a much higher annual lung cancer mortality risk of 1×10^{-3}. This risk is comparable to the yearly chance of a fatal injury among workers in the manufacturing industry or the government sector.[15]

The use of numbers such as these can give an unwarranted sense of security. They are extrapolated from animal data with all the variability that brings; for cancer, the shape of the dose–response curve, with inadequate exposure and

dose data, then derived by different statistical and stochastic models, has a profound effect on the calculation of risk. Knowledge of delivered as opposed to administered dose will greatly alter the risk estimate if there are protective barriers or detoxifying mechanisms for the chemical, as for formaldehyde or NTA. The mechanism of action can strongly influence the dose–response. Risk management requires that we develop risk estimations in this fashion, but we should not be deluded, nor delude the public, that the science is exact.

In addition to the frailties of biological data are the uncertainties in scientific observations. Diagnosis of neoplastic lesions has a subjective element and is affected by such factors as degree of autolysis, tissue preservation and fixation, as well as the distinction between benign and malignant lesions. With biological data, there is always an observer factor like the uncertainty principle in physics.

An example can be drawn from the environmental contaminants dioxins and furans. Clearly 2,3,7,8-tetrachlorinated dibenzo dioxin (TCDD) is an animal carcinogen, but there are few chronic toxicity data available for risk assessment and the choice of assumptions and the methodology used can profoundly affect the results obtained. Hickman[16] has pointed out that when the potency of 2,3,7,8-TCDD is compared to that of other polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) to calculate the toxic equivalent factor for a mixture of PCDDs/PCDFs, the resulting virtually safe dose or acceptable daily intake as calculated by different agencies can range from 0.007 pg/day for the U.S. EPA to 10 pg/day for the Canadian Department of National Health and Welfare, depending on the assumptions made as to mechanisms of toxicity, extrapolation to humans, and such. Thus, there can be a 1000-fold difference in estimates based on the same data. This is for compounds where there has been no adequate demonstration to date that human populations have suffered excess cancer.

Science cannot always give the clear, definite answers that the media and the public expect. The limitations and the strengths of science must be better appreciated as we develop our risk assessment process.

International Aspects

The International Program on Chemical Safety (IPCS) is a cooperative program of the World Health Organization, the International Labour Office, and the United Nations Environment Program established in 1980 and now with over 30 countries participating. The IPCS has close relationships to the Organization of Economic Cooperation and Development, the Commission of the European Communities, and the Food and Agriculture Organization. The objectives are largely devoted to risk assessment for chemicals covering estimation of their risk to human health and the environment and method development for risk evaluations. Products from the IPCS include environmental health criteria documents, health and safety guides, international chemical safety cards, poison information monographs, acceptable daily intakes for food additives, and pesticides. These are all used by member states to set their standards for safe levels of chemicals in food, air, drinking water, the workplace, and the environment.

Risk management is entailed in the IPCS objectives devoted to the prevention and response to chemical emergencies and accidents. New proposals that will probably be considered at the United Nations Conference on Environment and Development in 1992 in Brazil envisage that the IPCS should take on a greater role in providing risk management advice and protocols to member states, particularly developing countries.

Risk Perception

If the future of risk estimation lies with advances in our understanding of the basic biochemical processes that underlie the toxicology of chemical–cell interaction, then the future of risk perception lies with understanding the psychology of our attitudes. The structured ordered system of risk assessment depends on rational argument and logical thought, and admirable though these qualities are, they are not necessarily overriding factors in our ultimate decision-making. The words "risk perception" are used to describe the subjective process by which we intuitively assess risk.[13] What may seem to experts to be the public's misjudgment of objective risk estimates may, in reality, be a reflection of deeply held social and cultural values. These fears and concerns must be understood by decision-makers if they are to gain public acceptance of risk management strategies — as those responsible for citing nuclear reactors and hazardous waste dumps have learned.

It is perhaps worthwhile to examine some incidents in Canada where, following Jung's aphorism, reason has been replaced by slogans. The most dramatic was certainly the public reaction to the government ban on the sale of urea formaldehyde foam insulation (UFFI) under the Hazardous Products Act in 1980. At that time, it was judged to be the appropriate regulatory mechanism to control a product that released formaldehyde, a chemical of known toxicity with recent evidence of carcinogenicity to rodents. What clearly was not realized was the dramatic effect such action would have on the house market. This served to fuel a hysterical reaction to the potential hazard of formaldehyde so that it became impossible to maintain a middle line that there was a risk but that it was not an overwhelming one. During the height of the campaign by irate UFFI home owners for compensation, articles appeared daily in the press, particularly in Quebec, which "fanned the flames." The phrase "Les Victimes de La Miuf" arose and ministers were pilloried. Hundreds of millions of dollars of public money has already been expended in compensation and lost taxes, and some 11

years later, there are still many cases outstanding in the courts against the Canadian government. The nature of the public response was clearly out of proportion to what was known of the potential hazard in 1980 and what has subsequently been confirmed by epidemiological studies.[17]

The psychopathology of this cause célèbre would require the combined skills of a behavioral psychologist, a psychiatrist, and a poet (for the latter are often the most sensitive to human emotions) to elucidate. What is clear, however, is that at some point the risk became unmanageable.

The nuclear disaster at Chernobyl occasioned much public concern, although Canadians received extremely low exposures. The total dose (55% ingested from milk and foods) for May and June of 1986 ranged from a high of 1.63 microsieverts in Vancouver to a low of 0.17 microsieverts in Toronto, with a national average of 0.58 microsieverts.[19] Estimates for 1 year of exposure give a national average of 2.3 microsieverts. Compared with the average annual exposure to background radiation from natural terrestrial and cosmic radiation of 440 to 790 microsieverts, one can see how relatively low these exposures were. The estimate of risk from the 2.3 microsieverts is on the order of 1 in 50 million cancer risk per lifetime. Yet, the Chernobyl incident raised more information requests than any other single topic in health protection over the last 20 years. The phone lines were blocked with more than 5000 calls.

Clearly, in neither instance were we successful in communicating to the public the magnitude and importance of the risks. Public concern did not dutifully follow the ordered analysis of risk. However, in the case of Chernobyl, it could be argued that by an open and informative policy the public were eventually reassured.

A more recent example can be drawn from our review of recombinant bovine somatotropin (BST), a biosynthetic version of the naturally occurring pituitary hormone in cows. Bovine somatotropin can increase milk production in dairy cows from 10% to 30% and is rapidly broken down by human digestive enzymes. It is under investigational trial across Canada, and in response to wide-spread public concern, milk from test animals in British Columbia, Alberta, and Ontario is not available for human use. In Europe, the furor has been even more pronounced. In West Germany, environmentalists have "manned the barricades" against the hormone-injected "turbo-cow." The recent National Institutes of Health Technology Assessment Conference[19] concluded that the composition and nutritional value of milk from BST-treated cows is essentially the same as that from untreated cows. Similarly, meat and milk from BST-treated cows are as safe as from untreated cows. We are in agreement with this evaluation, yet at present, the public perception of risk for this biotechnology product has overwhelmed the scientific community.

What then can we learn from these cases? At the simplest level, we learn that the scientific analysis of a hazard is only acceptable up to a certain point. When the level of concern reaches irrational proportions, no amount of sound careful ratiocination will assuage the public's fears. Deeply held human emotions become impervious to the reasoned approach of experts.

Therefore, those involved in risk decisions should learn to recognize the warning signs when slogans overtake reason. The Canadian experience of Chernobyl shows that it can be done. Increasingly, the public receives its information through media other than print and so sensationalism and emotional engagement are emphasized. Print is a more intellectual medium that lends itself to scientific analysis. The challenge that risk managers face is to understand and appreciate public concerns and direct them to logical argument and sober consideration. The more we know of the psychology of risk perception, the better prepared we will be to deal with these most difficult, and often most political, situations.

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Civil and Criminal Liability for Violation of Environmental Laws

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Over the past several years, increasing public attention has been focused on environmental pollution at facilities owned or operated by the United States Government, with particular emphasis on hazards that pollution may present to human health and the environment. In response to the concerns which are being raised, federal officials and private citizens have investigated a variety of options they have available to ensure environmental laws are being enforced and to compensate those injured by the pollution. More and more, those options have included litigation. Criminal prosecutions have been instituted against government employees, and civil suits have been filed against the government, against those who contributed to the perceived problem and against those who are endeavoring to clean up the sites. Questions have been raised about whether, and to what extent, the government should indemnify its contractors or contractors should indemnify the government. Pending legislative initiatives may address some of these problems, but potential civil and criminal liability will probably be the order of the day for the foreseeable future.

Introduction

Most environmental laws, state and federal, contain provisions that impose civil and criminal liability on "persons" who violate those laws. The term "person" is defined in these statutes to include individuals. There are a number of recent cases in which state or federal officials have sought to impose liability on individuals for environmental law violations, even though, at the time of the violations, the individuals were employees of corporations of other entities. These efforts to impose civil or criminal penalties have occurred, primarily, in two situations: 1) when the circumstances of the case are particularly egregious (e.g., extremely hazardous toxins, toxic waste dump sites, or sustained noncompliance) and the defendants are high-ranking corporate officials of closely held corporations who have retained hands-on management of environmental issues or 2) where the enforcement authority wants to get the attention of the polluters and make a statement, political or otherwise (e.g., the criminal prosecution of three civilian government employees at the Aberdeen Proving Grounds in Maryland, to make the point that the government is not exempt from environmental laws).

Cases interpreting some of the environmental statutes have held that the individuals who may be liable for penalties are those who are "responsible" for the activities that gave rise to the violation. In fact, an occasional case has sought to impose liability on a relatively low-level employee. However, as has been noted, the usual approach when employees are singled out is to target the high-ranking officer in the organization.

A recent state and regional summary by the U.S. Environmental Protection Agency (EPA) of civil and criminal enforcement activity is set out in Tables I and II. Continued negative publicity regarding violations of environmental laws will most likely result in increased enforcement activity. Although recent legislation has severely restricted the circumstances under which federal employees can be held civilly liable for violations of environmental laws, there is no such protection against criminal liability, and the possibility of criminal prosecution is still a very real threat.

The Statutory Framework

The Resource Conservation and Recovery Act (RCRA)[A] is the major federal statutory authority for the regulation of waste. There are essentially three programs under RCRA that impose obligations on the generation, treatment, storage, and disposal of waste materials: Subtitle C, which deals with hazardous waste (as defined); Subtitle D, which deals with nonhazardous solid waste; and Subtitle I, which imposes certain requirements on underground storage tanks.

For enforcement purposes, it should be noted that RCRA is a program which Congress has permitted to be enforced by the states, if certain statutory requirements are met. As of July 1990, 46 states and several territories were administering all or a part of the RCRA program within their jurisdictions. Therefore, enforcement of RCRA violations will usually come from the states. However, in certain cases, EPA may

[A]The general descriptions of several of the regulatory schemes are summarized from an excellent publication of the National Association of Attorneys General, *State Attorneys General Guide to Environmental Law 1990*. State laws may vary and should be consulted for particular requirements.

TABLE I. Fiscal Year 1990 State-by-State Enforcement Data Summary

	Administrative Actions		
	EPA	State	Total
Most Prosecuted Violations			
CWA	1342	1236	2578
CAA	221	1581	1802
RCRA	362	1350	1712
SDWA	111	1055	1166
	149	1004	1153

	EPA Administrative Action			
	CAA	CWA	RCRA	UIC/PWS[A] SDWA
Region I	75	120	134	23/28
Region II[A]	302	328	284	18/318
Region III	307	83	203	8/236
Region IV[A]	327	635	271	66/82
Region V	160	271	189	894/104
Region VI[A]	175	784	245	52/38
Region VII	81	84	136	33/122
Region VIII	62	43	103	54/66
Region IX	274	106	77	15/116
Region X	39	124	70	3/45

[A]Criminal referrals of underground injection control (UIC)/public water supply (PWS)
CWA = Clean Water Act; CAA = Clean Air Act; RCRA = Resource Conservation and Recovery Act; SDWA = Safe Drinking Water Act.

have primary enforcement authority. Finally, to complicate matters further, there are certain conditions under which EPA will take an enforcement action, even when a state has primary responsibility for the RCRA program, such as when EPA feels the state is not acting expeditiously, the proposed resolution of the matter is inappropriate, or when a case may establish precedent.

Hazardous Waste[B]

Overview. Pursuant to §3002 of RCRA, 42 U.S.C. §6922, EPA has established requirements for generators of hazardous wastes. Those requirements set out the recordkeeping obligations of generators; they mandate the use of appropriate waste containers and the labeling for those containers; they designate the use of a Uniform Hazardous Waste Manifest System to ensure that hazardous waste is listed on a proper invoice for transportation and is designated to arrive at a permitted Treatment, Storage and Disposal (TSD) facility.

Regulations promulgated pursuant to §3003 of RCRA, 42 U.S.C. §6923, govern hazardous waste transporters. These regulations mandate 1) proper recordkeeping for transported waste; 2) transportation of hazardous waste only if properly labeled; 3) compliance with the manifest system; and 4)

[B]Hazardous wastes are either listed by the EPA, or they have certain characteristics, such as flammability, reactivity, corrosivity, or they fail to pass a particular EPA-developed test, the TCLP.

TABLE II. Civil and Criminal Referrals

	Total EPA/State Civil Referrals				Total EPA Criminal Referrals			
	CAA	CWA	SDWA	RCRA	CAA	CWA	SDWA	RCRA
Region I	9/7	6/22	0/2	2/5	1	3	2	2
Region II	8/1	3/18	0/2	0/0	1	2	1	0
Region III	8/26	8/21	0/1	0/8	2	4	1	2
Region IV	4/16	9/56	5/47	2/4	3	6	0	5
Region V	26/74	11/54	6/21	6/10	0	2	0	2
Region VI	10/5	17/0	1/84	3/2	0	2	1	6
Region VII	3/13	1/57	0/8	0/20	0	0	0	0
Region VIII	5/18	3/19	4/5	3/5	0	0	0	5
Region IX	12/6	2/2	0/8	1/1	0	1	0	0
Region X	6/23	1/0	0/3	1/1	2	3	0	0

CWA = Clean Water Act; CAA = Clean Air Act; RCRA = Resource Conservation and Recovery Act; SDWA = Safe Drinking Water Act.

transportation only to permitted TSD facilities.

Regulations under §3004 of RCRA, 42 U.S.C. §6924, govern owners and operators of TSD facilities. The standards established here include those for proper recordkeeping for the wastes being handled; compliance with the manifest system; treatment, storage, and disposal using EPA-approved methods; contingency plans for unanticipated damages resulting from the waste; proper maintenance of facility operations; and the providing of personnel training.

Each TSD facility must have a permit. The permit will contain, among a number of other enforceable requirements, facility-specific technical standards and provisions which require corrective action (i.e., cleanup) measures, to address leaks from waste management units. Although some facilities have final RCRA permits, most facilities still operate under "interim status" permits, which were authorized under RCRA under certain circumstances, until final permitting could occur.

The 1984 Amendments to RCRA added several features that have been the subject of increased regulation over the last several years. These have included: 1) the banning of land disposal of certain toxic materials, unless specifically approved by EPA; 2) the enhancement of EPA and state ability to enforce corrective action measures at RCRA facilities; and 3) the reduction in the amount of waste that can be generated, without the imposition of certain requirements.

Enforcement. Section 3008 of RCRA, 42 U.S.C. §6928, provides RCRA's enforcement authority for Subtitle C. Although state enforcement processes and penalties need not be identical to RCRA, many of them are very similar.

Under §3008, EPA may issue an administrative order assessing civil penalties, or requiring compliance, or both. Civil actions may also be instituted in court, by the Justice Department. Civil penalties of up to $25,000 per day of violation of the Act or administrative orders are authorized. Failure of a facility to comply with corrective action orders can also result in a $25,000 fine for each day of noncompliance.

On the criminal side, the maximum sentence for knowingly transporting or causing transport of a hazardous substance to an unpermitted facility, or for knowingly treating, storing, or disposing of hazardous waste without a permit, in violation of a permit condition, or in violation of interim status regulations, is 5 years' imprisonment and a $50,000 fine for each day of violation. For those who fail to file, or falsify required reports, manifests, applications or records, who transport without a manifest or who improperly export a hazardous waste, the maximum prison sentence is 2 years.

Both civil and criminal penalties can be imposed against any "person." That term is defined in §1004 of RCRA, 42 U.S.C. §6903, as:

> ". . . an individual, trust, firm, joint stock company, corporation (including a government corporation), partnership, association, state, municipality, commission, political subdivision of a state, or any interstate body."

There are also so-called "knowing endangerment" crimes under §3008(e) of RCRA. If a person commits a violation of RCRA, knowing that such violation places another person in imminent danger of death or serious bodily harm, that person may be fined $250,000 ($1,000,000 for an organization), and imprisoned for up to 15 years.

Nonhazardous Wastes

Overview. Despite the fact that the vast majority of waste generated in the United States is classified as nonhazardous waste (even though it may contain some hazardous waste), Subtitle D of RCRA is primarily an advisory, rather than a mandatory, subtitle. Essentially, according to its terms, Subtitle D was enacted to encourage and assist states in developing comprehensive plans for handling nonhazardous solid waste, using methods that are environmentally sound and that maximize the use of materials recoverable from waste. Thus, under Subtitle D, states are not required to obtain EPA approval for their nonhazardous solid waste management programs and EPA does not implement such programs in the states. About half the states do have EPA approved plans, which meet the minimum requirements of §4003 of RCRA, 42 U.S.C. §6943. Those requirements include the prohibition of new open dumps within the state and mandate that all solid waste in the state be used for resource recovery, or be disposed of in a sanitary landfill, or in an otherwise environmentally sound manner. Two areas in which EPA has recently moved to tighten standards, in order for states to have their programs qualify for EPA approval, are landfills and waste incineration. Stricter criteria have been proposed for each.

Enforcement. All states have some type of nonhazardous waste management program and may have a variety of civil and criminal penalties available to them under those nonhazardous waste statutes. Determination of individual liability is on a state-by-state basis.

There is one penalty provision in RCRA which may be applied, by the federal government, in cases involving solid waste (as well as in cases involving hazardous waste). That provision is §7003, U.S.C. §6973. Section 7003 provides that the EPA may sue any person who is contributing or has contributed to the handling, storage, treatment, transportation, or disposal of solid or hazardous waste which has or may present an imminent and substantial endangerment to health or the environment. The Administrator may seek appropriate relief in such a suit. The Administrator may also issue such orders as may be necessary to protect public health and the environment. A fine of $5,000 per day of violation of such an order is authorized.

Underground Storage Tanks

Overview. Subtitle I of RCRA governs all petroleum products stored in underground storage tanks (USTs)[C] and of any substance defined as hazardous under CERCLA. A UST is defined as one with at least 10% of its volume buried below the ground. The major provisions of the UST program are 1) a ban on the installation of corrodible tanks (effective May 7, 1985), 2) the initiation of a tank notification program, and 3) development of technical standards for all tanks.

Reports are to be made to a designated state or local agency on the age, size, type, location, and uses of tanks. Those who must report are distributors of regulated substances, owners of operational tanks, and owners of tanks taken out of service later than 1974, but still in the ground. Federal and state personnel are authorized to request pertinent information from tank owners; inspect and sample tanks; and monitor and test tanks, surrounding soils, air, surface water, and groundwater.

Enforcement. Civil penalties of up to $10,000 per day of violation, per tank, are authorized. There are no criminal penalties authorized for failure to notify, for false information, or for improper release detection, prevention, or correction. The EPA may issue compliance orders for any violations and the penalty for violation of these is $25,000 per day of continued noncompliance. States can obtain approval for enforcement, and as in Subtitle C, the enforcement provisions do not have to be identical to the federal provisions.

The Clean Water Act

Overview

Section 301(a) of the Clean Water Act (CWA), 33 U.S.C. §1311(a), prohibits the discharge of pollutants from a point source, as defined, into the navigable waters of the United States, unless the discharger holds a National Pollutant Discharge Elimination System (NPDES) permit, pursuant to Section 402 of the Act, 33 U.S.C. §1342. These permits establish the "effluent limits" for each pollutant discharged from a facility. The term "pollutant" is broadly defined in the statute, and the terms "point source" and "navigable waters" have been very broadly defined by the courts. Section 308 of CWA, 33 U.S.C. §1318, also requires that the NPDES permit specify the frequency and type of monitoring an operation must perform to determine its water quality, and it mandates that the Discharge Monitoring Reports (DMRs) generated by that monitoring be filed with the appropriate state agency.

Section 307(b) of CWA, 33 U.S.C. §1317(b), requires the pretreatment of industrial wastewater that may damage, interfere with, or pass through publicly owned sewage treatment works, or which may contaminate sludge.

Section 404 of CWA, 33 U.S.C. §1344(a), requires a permit for the discharge of dredge and fill materials into navigable waters. The U.S. Army Corps of Engineers administers this program.

Section 311 of CWA, 33 U.S.C. §1321, prohibits the discharge into navigable waters of oil or hazardous substances that may be harmful. In addition, a person in charge of a facility or a vessel from which oil or a hazardous substance is released in excess of the "reportable quantity," as defined, is required to report that release to the National Response Center immediately.

Enforcement

Thirty-nine states have the authority to issue and enforce NPDES permits, and in those states, state enforcement is the rule and EPA enforcement the exception. The EPA does have the authority, however, to review a state enforcement action to determine if it is adequate. In those cases, EPA may decide to "overfile" on the state case.

Most efforts to enforce CWA have been in the form of administrative action and with the use of civil penalties. Section 309 of the statute, 33 U.S.C. §1319, provides that EPA may issue a compliance order or file a civil suit for any violations of water quality-related effluent limitations, national performance standards, toxic effluent standards, or pretreatment standards, or for violations of any permit condition or limitation, either under an NPDES permit or a dredge-and-fill permit. Orders may be issued or suits filed for any violation of recordkeeping, monitoring, sampling, or reporting requirements.

Administrative penalties can amount to $10,000 per violation, up to a maximum total of $125,000 for some types of violations. The judicial penalty can amount to $25,000 per day.

Criminal penalties are established for three types of conduct: negligent violations, knowing violations, and knowing endangerment.

Any person who negligently violates effluent limitations, standards, permit conditions, (NPDES or dredge-and-fill), or who discharges oil or hazardous substances into the navigable waters is liable for a fine of not less than $2,500 nor more than $25,000 per day of violation, or by imprisonment for not more than 1 year, or both. Knowing violations may result in up to 3 years in prison and fines of $5,000 to $50,000. Second offences for both negligent and knowing violations receive double the penalties.

Any person who knowingly makes any false statement, representation, or certification in any application, record, report, plan, or other document or knowingly renders inaccurate any monitoring device or method required to be maintained is liable for a fine of not more than $10,000, or by imprisonment for not more than 6 months, or by both.

Anyone who fails to notify the National Response Center

[C] 42 U.S.C. §6991-6991(i).

of a spill of oil or a hazardous substance is subject to a fine of up to $10,000 and a prison term of up to 1 year.

If a person, in violating the Act, knowingly places another in imminent danger of death or serious bodily harm, that person could receive a the maximum penalty of a 15-year prison sentence and a $250,000 fine ($1,000,000, if the party is an organization).

Any person who is the owner, operator, or person in charge of a vessel, onshore facility, or offshore facility from which oil or a hazardous substance is discharged in violation of the Act is liable for civil penalties of up to $3,000 per barrel of oil or unit of reportable quantity of hazardous substance.

For purposes of civil penalties, a person is defined in Section 502 of the Act, 33 U.S.C. §1362, to include: "... An individual, organization, partnership, association, state, municipality, commission, or political subdivision of a state, or any interstate body." For criminal purposes, the term "person" also includes "any responsible corporate officer" [33 U.S.C. §1319(c)(6)].

The Clean Air Act

Overview

The Clean Air Act (CAA), amended substantially in 1990, regulates emissions to the atmosphere from both stationary and mobile sources. Under Section 109 of the CAA, 42 U.S.C. §7409, the EPA is to establish the highest level of various air pollutants in the ambient air that will not harm human health and set air quality standards at or below that level. These standards are known as Primary National Ambient Air Quality Standards (Primary NAAQSs). There are also Secondary NAAQSs, which are levels that must be maintained to protect public welfare from known or anticipated adverse effects (e.g., damage to animals, crops, and personal property). NAAQSs currently exist for carbon monoxide, sulfur dioxide, ozone, particulate matter, lead, and oxides of nitrogen.

The states are to establish procedures by which the NAAQSs are to be met. They do this by submission (and approval by EPA) of State Implementation Plans (SIPs), which outline how each air quality control region in the state will maintain compliance with the NAAQSs. These SIPs contain emissions limitations by source, schedules, and timetables for compliance, a permit program and assurances regarding enforcement of the program. If EPA disapproves of the plan, it must prepare a federal implementation plan (FIP) for the state.

Section 111 of the CAA, 42 U.S.C. §7411, requires EPA to establish standards for performance for new stationary sources. In areas that have attained the NAAQSs ("attainment areas"), there are so-called "prevention of significant deterioration" (PSD) provisions, which contain requirements concerning the protection of air in those areas. Persons planning to construct new sources or substantially modify existing sources in those areas must obtain a permit that contains emissions limitations based on the use of "Best Available Control Technology" for that source.

Under Section 112 of the CAA, 42 U.S.C. §7412, EPA is obliged to establish emissions standards for certain hazardous air pollutants. Prior to the 1990 Amendments, EPA had only listed eight substances as hazardous air pollutants — asbestos, benzene, beryllium, coke oven emissions, inorganic arsenic, mercury, radionuclides, and vinyl chloride — and had set emissions standards for only six. Under the 1990 Amendments, however, EPA has been directed to set industry-by-industry standards for 189 toxic air pollutants based on "maximum achievable control technology" (MACT), a technology level that permits economic considerations to be taken into account, unlike the preamendment §112.

The 1990 Amendments also require that various sources of air pollution obtain permits to ensure compliance with CAA requirements. These permits will be modeled on the CWA permits, and the program is designed to be operated by the states, as is the CWA permit program.

Enforcement

Civil. CAA provides that in the case of any person who is the owner or operator of an affected source, a major emitting facility (as defined) or a major stationary source (as defined), EPA may issue an administrative order or seek, in a judicial proceeding, a civil penalty of up to $25,000 per day of violation, for the following:

1. A violation of any requirement or prohibition of an applicable implementation plan or a permit.
2. A violation of other requirement or prohibition set out in Subchapter I, dealing with air quality and emissions limitations (including, among other things, new source performance standards, recordkeeping, inspections, monitoring, and entry; stack heights, public notification, and solid waste combustion); prevention of significant deterioration of air quality; visibility protection; and requirements for all nonattainment areas; Section 7603 of Subchapter III, dealing with willful violation or failure or refusal to comply with emergency orders; Subchapter IV, dealing with noise pollution and acid rain; Subchapter V dealing with permits, or Subchapter VI, dealing with stratospheric ozone protection.
3. Attempting to construct or modify a major stationary source in an area in which the Administrator determines that there is a prohibition against such activity.

Criminal. CAA provides that any person who knowingly violates any of the above requirements is subject to a fine, or by imprisonment not to exceed 5 years, or both. If the person has been previously convicted, the maximum fine and

period of imprisonment may be doubled.

Any person who knowingly 1) makes false material statements; 2) fails to report; or 3) falsifies or tampers with any monitoring device is subject to a fine, or imprisonment not to exceed 2 years, or both. If the person has been previously convicted, the maximum fine and term of imprisonment may be doubled.

Any person who negligently releases a listed hazardous substance into the air and places another person in imminent danger of death or serious bodily injury is subject to a fine, or imprisonment not to exceed 1 year, or both. If the person has been previously convicted for a similar crime, the maximum fine and punishment may be doubled.

Any person who knowingly releases a listed hazardous substance into the air and places another person in imminent danger of death or serious bodily injury shall, upon conviction, be punished by a fine and imprisonment of not more than 15 years, or both. An organization shall be subject to a fine not to exceed $1,000,000 per violation. If the person has been previously convicted under this section, the maximum fine and punishment may be doubled.

Definition of "Operator" and "Person" in the Clean Air Act

For purposes of civil and criminal liability under the 1990 Clean Air Act Amendments, Congress set out, in some detail, exactly who it meant to cover, as an operator. Also, for purposes of negligent releases of listed hazardous substances that place others in imminent danger of death or serious bodily injury, the term "person" is defined. Because Congress was so specific and because this may be the precursor of things to come, the provision, 42 U.S.C. §7413(h), is set out below, in some detail:

> "(h) Operator. For purposes of the provisions of this section and section 120, the term 'operator,' as used in such provisions, shall include any person who is senior management personnel or a corporate officer. Except in the case of knowing and willful violations, such term shall not include any person who is a stationary engineer or technician responsible for the operation, maintenance, repair, or monitoring of equipment and facilities and who often has supervisory and training duties but who is not senior management personnel or a corporate officer. Except in the case of knowing and willful violations, for purposes of subsection (c)(4) of this section, the term 'a person' shall not include an employee who is carrying out his normal activities and who is not a part of senior management personnel or a corporate officer. Except in the case of knowing and willful violations, for purposes of paragraphs (1), (2), (3), and (5) of subsection (c) of this section the term 'a person' shall not include an employee who is carrying out his normal activities and who is acting under orders from the employer."

The Comprehensive Environmental Response, Compensation and Liability Act

Overview

The Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), or the Superfund Act, is Congress' attempt to deal with the nation's abandoned and inactive waste sites. In the Act, as originally passed in 1980, Congress directed that the EPA establish a list of the 400 worst abandoned waste sites and to add additional sites to that list, as information about their hazards became available. At the present time, about 1200 of the approximately 30,000 identified abandoned waste sites have been placed on this so-called National Priorities List (NPL).

In CERCLA, Congress established a federally financed cleanup fund and authorized use of that fund (the so-called Superfund) to pay the cleanup costs of NPL sites, if necessary. However, the law is clear that, whether a site is on the NPL or not, whenever possible, the parties liable for the contamination are to perform the cleanup themselves or, in the alternative, pay the bill.[D]

Section 107 of CERCLA, 42 U.S.C. § 9607, provides that when a release or threatened release of hazardous substances (as defined) occurs, resulting in the incurrence of cleanup costs, the state or federal government (depending on which has been designated the "lead" agency) can seek reimbursement from a variety of potentially responsible parties (PRPs). They include: 1) the owner or operator of the vessel or facility from which the release occurred or may occur; 2) any person who, at the time of disposal of any hazardous substance owned or operated the facility at which the hazardous substance was disposed; 3) any person who arranged for disposal or treatment of a hazardous substance at the facility; and 4) any person who accepted the hazardous substances for transport to the disposal or treatment facility. Section 106 of CERCLA, 42 U.S.C. §9606, also provides for the federal government to seek injunctive relief, or to force cleanup by the parties themselves. This enforced cleanup may be accomplished in one of two ways: 1) by an administrative order to compel the PRPs to perform the cleanup themselves or 2) by a suit in federal court to compel cleanup. CERCLA also, in Section 107(a)(c), 42 U.S.C. §9707(a)(c), establishes the right of natural resources trustees to sue PRPs for damages to natural resources.

CERCLA also provides that it is illegal not to report the disposal of a hazardous substance in excess of the "reportable quantity" established for that substance.

[D] A number of states also have "mini-superfund" laws or other state statutory cleanup authority.

Enforcement

As has been noted, with respect to civil liability, CERCLA, in §107, 42 U.S.C. §9607, provides for the payment of response costs (including removal and remediation) by the parties responsible for the contamination, and for damages for injury to, destruction of, or loss of natural resources, so long as those costs are consistent with the National Contingency Plan. With respect to the reporting requirements, CERCLA provides that any person in charge of a vessel or facility at which a release, in excess of the reportable quantity, occurs, and who knows of that release, is required to report the release immediately to the National Response Center. Anyone who does not do that is subject to an administrative or a judicial penalty of up to $25,000 per day of violation; second and subsequent violations subjects the violator to a penalty of up to $75,000 per day. Destruction of required records, violations of financial responsibility requirements, and violation of administrative orders, consent decrees, and settlement agreements are subject to the same penalties.

Interference with any effort by the government to gain access to property or gather information about the property may result in a penalty of $25,000 per day of noncompliance. Interference with or refusal to comply with removal or remedial actions can result in the imposition of damages of up to three times the costs incurred by the Superfund.

On the criminal side, CERCLA provides that any person in charge of a vessel or facility at which a release, in excess of the reportable quantity, occurs faces a fine assessed in accordance with Title 18 of the U.S. Code and/or up to 3 years in prison (5 years for a second offense) for failure to report the release immediately. Destruction of required records carries the same penalty.[E]

The Emergency Planning and Community Right-To-Know Act

The Emergency Planning and Community Right-to-Know Act (EPCRA), or Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986, 1) creates state and local mechanisms for the dissemination of information about hazardous chemicals in workplaces and 2) mandates planning for what to do in the event such chemicals are released into the environment.

There are four essential requirements of EPCRA, as follows: 1) emergency planning; 2) emergency release notification; 3) community right-to-know reporting requirements; and 4) toxic chemical release reporting (emissions inventory).

[E]Knowing failure to report the existence of a facility at which hazardous substances were stored, treated, or disposed within 180 days of the passage of CERCLA, was punishable by a fine of up to $10,000 or a 1-year jail sentence.

Emergency Planning

Under Section 301 of EPCRA, 33 U.S.C. §11001, the Governor of each state was to appoint a State Emergency Response Commission (SERC) which, in turn, was to appoint Local Emergency Planning Committees (LEPCs). The major duty of each LEPC was to develop an emergency response plan for its planning district. That plan was to identify each facility within the district subject to the requirements of Subtitle I of the Act; identify transportation routes for extremely hazardous substances (as defined); describe emergency response procedures; designate a community coordinator and facility coordinators, to make decisions necessary to implement the plan; and describe methods for determining the occurrence of a release and the probable affected areas and outline evacuation plans. The SERC was to review those local plans and establish procedures for receiving and processing public requests for information.

In Section 302 of EPCRA, 33 U.S.C. §11002, Congress directed the Administrator of the EPA to publish a list of "extremely hazardous substances" (EHSs) and establish a threshold planning quantity for each substance. EPA has currently designated about 366 EHSs. As a rule, a facility that produces, uses, or stores any of these substances in quantities greater than the threshold planning quantity must notify the SERC or LEPC within 60 days that it is subject to the requirements of the Act.

Emergency Release Notification

When a release of an EHS occurs, in excess of the reportable quantity designated for that substance, the SERC or LEPC must be notified.

Community Right-to-Know Requirements

Section 311 of EPCRA, 33 U.S.C. §11021, provides that facilities (Standard Industrial Classification [SIC] Codes 1–89) which have hazardous chemicals present at the facility must obtain or develop a Material Safety Data Sheet (MSDS) for each such chemical. Those MSDSs, or a list of chemicals for which MSDSs are required, must be submitted to SERCs and LEPCs, if the facility has more than a threshold quantity (established by EPA).

Section 312 of EPCRA, 33 U.S.C. §11022, requires the submission of chemical inventory forms to SERCs, LEPCs, and local fire departments, if the facility, at any time during the preceding calendar year, had more than a defined threshold quantity of substances for which they were required to maintain MSDSs.

The reporting requirements under §312 are two-tiered. Tier I information is submitted annually on the quantities and general location of various categories of chemicals. Tier II reporting, which may be required by a state or by local citizens, is more specific. It requires individual chemical names, manner of storage, and location of the chemical in the

facility.

Toxic Chemical Release Reporting

Section 313 of EPCRA, 33 U.S.C. §11023, requires that EPA establish an inventory of toxic chemicals requiring the reporting of routine releases, as opposed to emergency releases. There are about 329 chemicals on that list. This report is required annually and is imposed only on facilities in SIC Codes 20–39 (manufacturing) with ten or more full-time employees and who manufacture, process, import, or use any of the chemicals in amounts greater than the threshold quantity established by EPA.

Enforcement

Section 325 of EPCRA, 33 U.S.C. §11045, provides for administrative proceedings and civil and criminal actions. State and local governments are authorized to bring actions against an owner or operator of a facility for 1) failure to notify under §302, 2) failure to provide information under §303, 3) failure to submit MSDS information as required by §311, and 4) failure to submit Tier I information required under §312.

There is a citizen suit provision as well, and that provision permits any person (including states and localities) to file suit against an owner or operator of a facility for failure to submit 1) follow-up reports, under §304; 2) MSDS submissions under §311; 3) Tier I information required under §312; and 4) toxic chemical release forms required under §313.

Individual Liability

A number of courts have imposed liability, both civil and criminal, on individuals for violations of environmental laws. Almost all courts have emphasized that these cases are fact- and statute-specific. However, in the recent past, a number of courts have not really engaged in the thorough type of analysis which, in our view, is necessary in order to reach the conclusion that individual liability is warranted.

Civil Liability

Most of the high visibility cases that have imposed personal civil liability have involved efforts to recover cleanup costs, for fairly egregious environmental contamination, from individuals who ran closely held corporations which are now insolvent.

Courts have been willing to impose this liability based primarily on two factors:

1. The very broad statutory language of such statutes as RCRA and CERCLA, which provide that individuals may be liable for a wide variety of violations.
2. The very strong policy, in those statutes, that those who created the pollution should pay to clean it up.

Many courts that have imposed liability (particularly cleanup costs) upon individuals under the environmental laws have done so primarily on the grounds that the liable official actually had personal involvement in the commission of the violation. This approach represents the simple application of the long-settled doctrine that tort liability extends to individuals in an organization who actually participated in wrongful conduct that resulted in damages.[F]

Some courts have demonstrated a willingness to impose liability, under these environmental laws, on "responsible corporate officials" who, while not directly participating in waste transportation, storage, treatment, or disposal, had overall responsibility for the facility at which the activities occurred. In some cases, courts have imposed liability upon individuals who were in charge of waste handling, storage, or disposal practices. However, even in those cases, a showing of frequent involvement and personal control has been required.

One of the first cases that imposed civil liability on individuals, under the specific terms of an environmental law, was *United States* v. *Northeastern Pharmaceutical and Chemical Co.*, 579 F. Supp. 823 (N.D. Mo. 1984), aff'd in part, rev'd in part, 810 F.2d 726 (8th Cir. 1986), *cert. denied* 484 U.S. 848 (1987). In that case, two corporate executives were held liable under both RCRA and CERCLA.

The RCRA count was brought under Section 7003, which imposes liability on "any person . . . who has contributed or who is contributing to . . . handling, storage, treatment, transportation or disposal" of hazardous waste that may pose an imminent and substantial endangerment to health or the environment. Under the circumstances of that case, two corporate officers were held personally liable because one actually arranged the waste transportation and disposal and the other had ultimate authority for Northeastern Pharmaceutical's operations and any decisions regarding that disposal. Both were deemed to have "contributed to" the waste disposal that created the "imminent and substantial endangerment." 810 F.2d at 745.

The court also found one of those corporate officers liable for cleanup costs under §107(a)(3) of CERCLA. That provision provides for strict liability, for specified costs of certain releases at sites covered by the Superfund Act. That liability extends to "any person who, by contract, agreement or otherwise, arranged for disposal or treatment of hazardous substances owned or possessed by such person . . . ." As was the case with the language of §7003 of RCRA, the court read

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[F]Courts have long held that corporate executives can be reached, for civil liability purposes, by the use of the long-settled doctrine of "piercing the corporate veil," when those executives essentially use the corporation as their "alter ego," by appropriating corporate assets to their own use, failing to observe corporate formalities, etc. This discussion does not really emphasize that theory but focuses on cases in which courts have imposed liability for conduct which did not rise to that level.

this language (and congressional intent to make those who created the pollution pay for its cleanup) broadly, to hold the official liable. It held that liability was not derivative, by virtue of the official's position in the corporation, but simply because he had personally "arranged for" the transportation and disposal of the hazardous materials.

Yet another theory of liability which has been invoked to establish personal liability is that the individual was an "operator," in statutes which have held that liability extended to "owners and operators."[G] One of the first cases to impose liability on this theory is *New York* v. *Shore Realty Corp.*, 759 F.2d 1032 (2d Cir. 1985), a CERCLA case. In that case, the court held that the individual was "in charge of the operation of the facility in question, and as such is an 'operator' within the meaning of CERCLA." 759 F.2d at 1052.

In making these sweeping statements, the court was backed by many facts demonstrating that particular individual's culpability. That individual had incorporated Shore Realty solely for the purpose of purchasing the property on which the hazardous waste was stored. He made, directed, and controlled all corporate decisions. Before purchasing the site, he was personally aware that the hazardous waste was being stored — illegally — at the site, and that Shore's environmental consultant had reported on the "sorry state" of the facility. Furthermore, after becoming aware of the environmental problems, Shore sought a waiver of environmental liability from the state, which was denied. Finally, the court found, "Shore did nothing about the hundreds of thousands of gallons of hazardous waste standing in the deteriorating tanks. In addition, although a growing number of drums were leaking hazardous substances, Shore essentially ignored the problem . . . ." Thus, the court had "easy" facts on which to base its finding of personal liability.

In another CERCLA decision, a court concluded that prior case law established that "[e]mployees of a corporation can be held personally liable under CERCLA for activities over which they had control and supervision." (Citing Northeastern Pharmaceutical and Shore Realty.) The court also summarized the factors that it believed had been considered in determining whether liability should be imposed on individuals, as operators. Those factors included:

1. Whether the person had the capacity to discover, in a timely fashion, the release or threat of release of hazardous substances.
2. Whether the person had the power to direct the mechanisms causing the release.
3. Whether the person or corporation had the capacity to prevent and abate damages.

United States v. *Carolina Transformer Co.*, 20 ELR 20935 (E.D.N.C. 1989).

Similarly, another court, noted that "[i]mposing liability on a corporate official is a serious matter, and because CERCLA provides no explicit way to distinguish, among corporate actors,[H] the courts should respond with proper standards." The court then went on to indicate that it would look at evidence of an individual's ability to control, among other things, waste handling procedures; the individual's position in the company and percentage of stock owned; evidence of responsibility for waste disposal practices, including actions and inaction; and efforts to prevent unlawful hazardous waste disposal. Thus, here, the focus is "whether the corporate official could have prevented (or significantly abated) the hazardous waste discharge at issue." *Kelley* v. *ARCO Industries Corp.*, 723 F. Supp. 1214 (W.D. Mich. 1989). Although some of the cases demonstrate the court's willingness to pursue a "responsible corporate official," the rule, even in those cases, clearly requires that frequent, hands-on contact is necessary.

In addition, some tribunals have been hostile to the "responsible corporate official" concept. For example, in *Riverside Market Development Corp.* v. *International Building Products, Inc.*, 931 F.2d 327 (5th Cir. 1991), the court said only that "CERCLA prevents individuals from hiding behind the corporate shield when, as "operators," they themselves actually participate in the wrongful conduct prohibited by the Act." In this case, the court held that the plaintiffs (in a private cost-recovery action) had not come forward with any evidence that showed the board chairman and 85% stockholder "personally participated in any conduct which violated CERCLA." He spent very little time at the plant operations, except to attend meetings and review financial statements; and there was no evidence he had the opportunity to direct or personally participate in the improper disposal of (the hazardous waste).

The concept of liability for an "owner or operator" of a facility is one that is also present in RCRA. A recent decision imposing individual operator liability for violation of RCRA requirements is *United States* v. *Conservation Chemical Company of Ill.*, 733 F. Supp. 1215 (N.D. Ind. 1989). In that case, the court held that four elements must be proved in order for liability to attach under §3008(a) of RCRA, 42 U.S.C. §6928(a):

1. The defendant is a "person," as that term is defined in §1004(15) of RCRA.
2. The defendant is an "operator" of the facility.

[G] If a corporation is the "owner" of a facility, such ownership would seem to eliminate that possibility for imposing individual liability.

[H] Indeed, this court, as have others, indicated that CERCLA does not explicitly address whether a court may hold a corporate official liable for cleanup costs.

3. The facility is a hazardous waste treatment, storage, or disposal facility subject to RCRA.
4. The defendant failed to comply with RCRA requirements applicable to operators of the facility.

The court indicated that the individual defendant was clearly a "person" as defined in the statute, and it also held that the defendant could be liable as an operator.[1]

Although the court did not really distinguish between the criteria it considered sufficient to hold the individual defendant liable as an actively involved corporate official and as an operator, it indicated that this individual could be held personally liable under both constructs when it was shown that the individual 1) was president, chairman of the board, treasurer, and principal stockholder; 2) designed the treatment processes at the facility; 3) visited the facility half to two-thirds of the working days each month, until he moved away; 4) called nearly every day, after he had moved, to discuss leaks, spills, and other aspects of the facility's operation and production; and 5) was responsible for environmental compliance. The court did note that the individual would not be liable as an actively involved corporate official for isolated occurrences done without his knowledge and contrary to company policy. However, clearly that had not happened here.

Other tribunals, however, have been quick to point out that, absent overwhelming control, individual liability should not attach, for violations of regulatory requirements, under the environmental laws. A very recent case before an EPA judicial officer involved a claim that a corporation, and its secretary–treasurer, as an operator, were both civilly liable for failure to perform the necessary steps, under 40 C.F.R. §265, to close an interim status surface impoundment. In the *Matter of Southern Timber Products, Inc., D/B/A Southern Pine Wood Preserving Co. and Brax Batson*, 1990 RCRA LEXIS 22 (USEPA 1990).

The judicial officer first rejected the idea that the individual defendant had, in some way, stepped out of his corporate role and conducted himself in such a way as to permit the imposition of liability by "piercing the corporate veil." He noted that the secretary–treasurer had not acted in such a way to make the corporation his alter-ego; the corporation was never undercapitalized; and the corporate assets were never treated as this individual's assets (i.e., he never added to or withdrew capital at will). In sum, sufficient attention was paid to maintaining the separate identity of the corporation to make it a bona fide corporate entity and not simply a facade to shield an individual business operation.

The judicial officer also held that there was no indication that the individual in this case was the "operator" of the facility in question. The regulations stated that the definition of "operator" was the "person responsible for the overall operation of the facility." The individual in this case did play a very significant role in the decisions regarding the facility's closure. However, the evidence also showed that the facility's plant managers were completely in charge of the plant operation; the Board of Directors had the authority to approve or disapprove capital expenditures; and the president had ultimate decision-making authority. In other words, although the individual may have been the Board's liaison to the facility, and he had some authority to engage in independent decision-making, he did not have sole responsibility for the overall operation of the facility. Rather, given the joint authority and responsibility exercised by the Board, the president, this individual, and the plant managers, the only clear conclusion to be drawn was that the facility operator was the corporation itself.

The judicial officer said:

> "Absent circumstances that justify a piercing of the corporate veil, the Agency may not reach beyond a corporate operator to impose liability for violations of Part 265 upon a corporate officer. Corporate operators of RCRA facilities necessarily rely upon individuals or groups, often corporate officers, to direct their activities, including activities that might lead to or constitute a RCRA violation.
>
> "Such reliance, however, does not justify disregard of the corporate form and imposition of personal liability. If decision-making authority provided a sufficient basis for imposing liability, any corporate officer or shareholder who makes a decision or directs an activity that is ultimately deemed to be a RCRA violation would be personally liable for the costs associated with achieving compliance, and for civil penalties of up to $25,000 per violation per day. Given the strict liability and substantial penalties that attend RCRA violations, as well as the sometimes confusing nature of the RCRA regulatory scheme, I am loath to impose such sweeping liability upon a corporate officer absent more compelling evidence that the officer is the owner or operator of the facility as defined in the rules."

The judicial officer also held that negligent conduct in pursuit of the cleanup, even if proven, could not, alone, be the basis for a finding of individual liability.

However, in a recent case, a court, in extending liability to an individual, found that there could be more than one "operator" of a landfill. In that case, the individual was listed on certain certificates required for regulatory compliance as the operator; he was one of the named lessees of the property

[1] An earlier decision in the same case had held the same individual, as a corporate officer, liable under RCRA, regardless of his status as an operator, as long as he was responsible for overall operation of the site, made decisions concerning environmental compliance, and was actively involved in the alleged violative activity. *United States* v. *Conservation Chemical Co.*, 660 F. Supp. 1236.

on which the landfill was located, and he remained personally liable on the lease; he exercised control over the landfill, along with its named manager; he and the named manager jointly decided who to hire; he personally decided whether improvements would be carried out; and he purchased equipment. In addition, he was the named insured on the landfill's insurance policy, and he personally guaranteed an open-ended loan to the landfill company. *United States* v. *Environmental Waste Control, Inc.*, 710 F. Supp. 1172 (N.D. Ind. 1989).

Criminal Liability

When criminal activity is alleged, even in the corporate context, individuals are generally charged with the crime. The main issue in this area of the law is how much evidence of knowledge is required, in order to sustain a conviction. As is the case on the civil side, reported cases in this area have generally involved egregious conduct and have, on the whole, focused on employees of small- to-medium-sized companies.

All of the environmental statutes have provisions that make certain types of conduct into criminal offenses. These provisions encompass negligent, knowing, and strict liability offenses. Selected provisions from CWA, RCRA, and CERCLA which illustrate each of these three types of offenses will be discussed.

Negligent Violation of the Clean Water Act

The CWA authorizes prosecutions for, *inter alia*, the negligent violation of any of its provisions and/or conditions in a NPDES permit, and it provides that those convicted "shall be punished by a fine of not less than $2,500 nor more than $25,000 per day of violation, or by imprisonment for not more than 1 year, or both."

In *United States* v. *Hoflin*, 880 F.2d 1033 (9th Cir. 1989), the defendant was convicted of aiding and abetting in the negligent violation of the NPDES permit pursuant to 33 U.S.C. §1319(c)(1). The Defendant had been the director of Public Works for a municipality that owned and operated a restaurant. He directed that certain waste be burned instead of complying with its disposal under the terms of the permit. In *United States* v. *Frezzo Bros. Inc.*, 602 F.2d 1123 (3rd Cir. 1979), the defendants were convicted of negligent violation of 33 U.S.C. §1319(c). The defendants were the principal corporate officers in a family business and maintained inadequate holding tanks for their waste water which, whenever it rained, would overflow and discharge into a stream.

In the recent case of *United States* v. *Boldt*, 929 F.2d 35 (1st Cir. 1991), the U.S. Court of Appeals for the First Circuit upheld a criminal conviction of an employee at an electroplating company for CWA violations. The evidence showed that industrial wastewater, containing metals in excess of the pretreatment limits, had been discharged to the city sewer. The evidence further showed that the employee, a chemical engineering manager, was responsible for controlling pollution from the plant; that he condoned or ordered a by-pass of the pollution control equipment; and that he could have shut down the plant, rather than ordering the by-pass. It was also shown that by-passing the pretreatment system was a very frequent occurrence at this plant and that the defendant had misled city representatives about the discharges. The court of appeals further held that the defendant was not entitled to a jury instruction that business or economic necessity prevented him from shutting down the plant.

Knowing Violation of RCRA

RCRA contains many provisions that involve knowing violations. However, courts are split over how much knowledge is required. The Third and Ninth Circuits have different knowledge requirements for a criminal violation of 42 U.S.C. §6928(d)(2)(A). Pursuant to 42 U.S.C. §6928(d), it is unlawful for any person to: knowingly treat, store, or dispose of any hazardous waste . . . without a permit . . . .

In *United States* v. *Johnson & Towers, Inc.*, 741 F.2d 662 (3rd Cir. 1984), the court identified a four-part knowledge requirement: that the defendant must know that he treated, stored, or disposed of a waste; that he knew the waste was hazardous; that he knew a permit was required; and that he knew no permit had been obtained. More specifically, the Court stated, "we conclude that . . . all the elements of that offense must be shown to have been knowing." 741 F.2d at 664-665.

In *United States* v. *Hoflin*, 880 F.2d 1033 (1989), the Ninth Circuit declined to follow the four-part knowledge requirement in *United States* v. *Johnson & Towers*. On appeal, Hoflin had argued that he did not know of the permit requirement. In other words, Hoflin maintained that knowledge of the lack of a permit was an essential element of the crime. In rejecting this argument, the Ninth Circuit reasoned that knowledge of the absence of a permit is not an element of the offense and that the government need only prove that the defendant knowingly disposed of the waste and that the waste was hazardous.

In the case of *United States* v. *Neville Chemical Co.*, 20 ELR 20197 (9th Cir. 1989),[1] a corporation appealed a conviction for knowingly disposing of hazardous wastes, in violation of §3008 of RCRA, 42 U.S.C. §6928(d)(2). That crime is established by a showing that 1) any person; 2) knowingly treated, stored, or disposed of any hazardous waste; 3a) without a permit; or 3b) in knowing violation of any material condition or requirement of such permit. The appeals court rejected the contention that this language re-

[1]This case was not authorized for publication in the Federal Reporter System and is generally not able to be cited as precedent. See Ninth Circuit Rule 36-3.

quires a finding of "specific intent" to violate the statute (i.e., that the court must find the defendant knew it had disposed of wastes, knew they were hazardous and knew there was no permit). The court held that the trial court need not find that the defendant knew the wastes were disposed of and that they were hazardous. Neither proof of knowledge of the law nor proof of intent were required.

In *United States* v. *Dee*, 912 F.2d 741 (4th Cir. 1990), cert. denied, 111 S. Ct. 1307 (1991), three civilian employees of the federal government, who were in charge of certain facilities at the Aberdeen Proving Grounds in Maryland, were convicted of several knowing violations of RCRA including unpermitted treatment, storage, and disposal of hazardous wastes. The defendants appealed the convictions, arguing that they did not "knowingly" commit the crimes with which they were charged.[K] The defendants argued that they did not know violation of RCRA was a crime or that regulations existed identifying the chemical wastes as RCRA hazardous wastes. The appeals court rejected that argument on the basis of the old chestnut, "ignorance of the law is no excuse." The court went on to quote from a Supreme Court case involving a conviction for transportation of some hazardous materials in violation of Interstate Commerce Commission regulations: "Where, as here . . . dangerous or deleterious devices or products or obnoxious waste materials are involved, the probability of regulation is so great that anyone who is aware that he is in possession of them or dealing with them must be presumed to be aware of the regulation."912 F.2d at 745, quoting *United States* v. *International Minerals and Chemical Corp.*, 402 U.S. 558 at 565 (1971).

The appeals court did agree that it was necessary for the government to prove the defendants knew the chemicals were hazardous, or "had the potential to harm others or the environment." However, the court noted that there was overwhelming evidence the defendants were aware they were dealing with hazardous chemicals and that they were "wastes," as that terms is used in RCRA. [See also *United States* v. *Sellers*, 32 ERC 1881 (5th Cir. 1991), holding it was not "plain error" for a court not to give an instruction that the defendant knew the waste was hazardous, when the defendant clearly knew he was disposing of paint solvent, which was extremely flammable.]

One of the defendants in *United States* v. *Dee* also argued he was not a person who "directed the storage or disposal operations." The appeals court rejected that argument, finding that he was in charge of operations at the facility where the chemicals were illegally stored and that he had originally ordered the placement of those chemicals in the nonpermitted facility.

[K]The defendants also argued that they were immune from prosecution because of their status as federal employees. The appeals court rejected that argument, noting that sovereign immunity does not immunize any federal employee from the operation of the federal criminal laws.

As in the civil area, efforts have been made to establish criminal liability on the basis that a person is a "responsible corporate official." However, these efforts have generally been unsuccessful because most environmental statutes require at least knowledge of some elements of the crime before a defendant can be criminally liable.

A recent case which discusses the knowledge requirement is *United States* v. *McDonald and Watson Waste Oil Co.*, 1991 WL 74173 (1st Cir. 1991). In that case, a corporation and several individuals were convicted of illegally treating, storing, transporting, and disposing of hazardous wastes without a permit; of transporting and causing the transport of hazardous waste to an unpermitted facility, all under RCRA; of failing to report the release of a hazardous substance, under CERCLA; and of making false statements and mail fraud, both under 18 U.S. Code.

All three individuals appealed their convictions. The appeals court upheld several of the convictions with very little discussion. Rejecting arguments that the defendants did not know the wastes were hazardous, it held that knowledge of the hazardous nature of the substances could be inferred from certain evidence which was offered at the trial. That evidence included discussions with and correspondence to the defendants and the presence of their signatures on certain documents. The court held that the jury could also infer, from the evidence, knowledge of the permit status of the facility or, at least, that the defendant had willfully failed to determine the status of the hazardous material under the permit.

However, the court did reverse the conviction of one defendant because the government had not proved he actually knew the shipments of hazardous waste were being made. In so doing, the court rejected the argument that the defendant could be convicted under environmental laws *which require knowledge* [emphasis added], solely on the basis that he was a "responsible corporate officer."

The court indicated that under some public welfare statutes (e.g., Food and Drug Act) conviction of a person may be based solely on a finding that the person had "authority with respect to the conditions that formed the basis of the alleged violations." *United States* v. *Dotterweich*, 320 U.S. 277 (1943) (upholding a misdemeanor conviction for the shipment of misbranded or adulterated food and drugs, even though the official had no knowledge of the shipment). The court noted, however, that crimes of this type are strict liability crimes. A person is guilty under such a statute if he had, by reason of his position in the corporation, responsibility and authority either to prevent, in the first instance, or promptly to correct, the violation complained of, and that he failed to do so. See *United States* v. *Park*, 421 U.S. 658 (1975).

However, if a statute imposes a knowledge requirement, knowledge must be proved. Said the *McDonald and Watson* court:

> "Knowledge may be inferred from circumstantial evidence, including the position and responsibility of defendants such as corporate officers, as well as information provided to those defendants on prior occasions. Further, willful blindness to the facts constituting the offense may be sufficient to establish knowledge. However, the district court erred by instructing the jury that proof that a defendant was a responsible corporate officer, as described, would suffice to conclusively establish the element of knowledge expressly required under §3008(d)(1) [of RCRA]. Simply because a responsible corporate officer believed that, on a prior occasion, illegal transportation occurred, he did not necessarily possess knowledge of the violation charged. In a crime having knowledge as an express element, a mere showing of official responsibility is not an adequate substitute for direct or circumstantial proof of knowledge."

See also *United States* v. *White*, 1991 WL 22878 (E.D. Wash. 1991). Court held that the government was required to prove not only knowing treatment, storage, or disposal of hazardous waste under RCRA, but it must also prove that the defendant knew the waste was hazardous.

It should be noted that some criminal provisions of some of the environmental statutes do not require proof of knowledge. For example, under the Clean Air Act, negligent endangerment of others by virtue of a release to the atmosphere is a crime.

Strict Liability Offense Under CERCLA

42 U.S.C. §9603(b)(3), in relevant part states:

> "... any person [in charge of a vessel or a facility] from which a hazardous substance is released, other than a federally permitted release, in a quantity equal to or greater than that determined pursuant to section 9602 of this title, who fails to notify immediately the appropriate agency of the United States Government as soon as he has knowledge of such release or who submits in such a notification any information which he knows to be false or misleading shall, upon conviction, be fined in accordance with the applicable provisions of Title 18 or imprisoned for not more than 3 years (or not more than 5 years in the case of a second or subsequent conviction), or both. Notification received pursuant to this paragraph or information obtained by the exploitation of such notification shall not be used against any such person in any criminal case, except a prosecution for perjury or for giving a false statement."

Section 9603(b) imposes strict liability upon the person in charge of a facility for the failure to report a release of hazardous substance as soon as the person knows of it. In *United States* v. *Carr*, 880 F.2d 1550, 1554 (2d Cir. 1989), a supervisor of maintenance at a rifle range was convicted under Section 103 of CERCLA, 42 U.S.C. Section 9603, for failing to report the improper disposal of waste cans of paint (an improper release) to the appropriate authorities. The court held that the meaning of "person in charge" under both Section 103 of CERCLA and Section 311 of the CWA, 33 U.S.C. §1321, encompassed "supervisory personnel who have responsibility for the facility." The bases for the court's decision were the legislative history of CERCLA and discussions contained in the Congressional Record.

Penalties

Penalties that are imposed for environmental crimes can also be quite severe. In the case of *United States* v. *Bogas*, 920 F.2d 363 (6th Cir. 1990), a court of appeals considered the issue of whether a trial court had improperly applied the federal sentencing guidelines. In that case, an airport manager had authorized the unpermitted burial of some hazardous waste on airport property. The action was soon discovered, and prompt remediation occurred. However, the court indicated that the cost of the cleanup necessitated a higher offense level than had been assigned. See also *United States* v. *Sellers*, 32 ERC 1881 (5th Cir. 1991) (41-month prison sentence upheld, based on an increase in sentencing level for "a discharge ... resulting in actual environmental contamination," even if the release was just for one day); *United States* v. *Wells Metal Finishing, Inc.*, 32 ERC 1505 (1st Cir. 1991) (upholding a 15-month prison sentence and a year of supervised release, conditioned in the payment of a $60,000 fine, for discharging excessive amounts of zinc and cyanide into a municipal water system, for 2 years, in violation of the Clean Water Act).

Immunity from Liability for Injuries

Traditionally, government employees have been spared liability for injuries occurring as a result of activities performed during the course of their employment. The Federal Tort Claims Act has been considered the traditional, and exclusive, legal mechanism by which persons, injured by negligent or wrongful acts of federal employees committed within the scope of their employment, have been compensated for their injuries.

In 1988, a Supreme Court decision changed this tradition. In *Westfall* v. *Erwin*, 484 U.S. 292 (1988), the Supreme Court restricted the common law tort immunity available to federal employees. In *Westfall*, officials of a federal storage depot were charged by a federal civilian warehouseman with negligence in "proximately causing, permitting, or allowing [the warehouseman] to inhale [injurious levels of] ... soda ash." id. at 294. The warehouseman claimed that he had suffered chemical burns to his eyes and throat due to his

inhalation of soda ash dust that spilled from a bag sent to his warehouse. The federal district court held that the federal officials were absolutely immune from liability for the tort actions committed while they were acting "within the scope of their employment." The U.S. Court of Appeals for the Eleventh Circuit reversed the decision, however. The Eleventh Circuit held that a federal employee enjoyed immunity only where the challenged action fell within the scope of his or her employment *and* the act was discretionary in nature. id. at 295 [emphasis added]. The Supreme Court affirmed the circuit court, refusing to adopt a broad view of the scope of immunity allowed to federal employees. id. at 297.

In response to the Supreme Court's decision, Congress enacted the Federal Employees Liability Reform and Tort Compensation Act of 1988. This Act specifically prohibits a suit against an individual federal employee, acting within the scope of employment at the time of the incident, whether the Act was discretionary or not. Congress enacted this Act with the purpose of protecting federal employees from personal liability for common law torts committed within the scope of their employment, while continuing to provide persons injured by the common law torts of federal employees with an appropriate remedy against the United States. H.R. 4358 100th Cong., 2d Sess. §2 (1988).

Again, it should be reiterated that Federal Employees are not immune from criminal prosecution/liability. See *United States* v. *Dee, supra.*

Topics in Chemical Risk Assessment

A Historical Review of the Need for Military Toxicology and the U.S. Army's Response

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"If men could learn from history, what lessons it might teach us!"

Samuel Taylor Coleridge
(1772–1834)

Is there a discipline called "military toxicology" that is different enough from the standard practice of toxicology to deserve a distinctive label, or is military toxicology merely the usual practice of toxicology on a military installation or on behalf of the military? To answer this question, I will historically review the requirements for toxicological assessments that occurred in the United States military services and a few foreign military services. How the U.S. Army fulfilled its need for toxicological studies through the establishment of several laboratories is discussed, followed by some thoughts for the future.

Introduction

The Early Years

Considering a traditional definition of toxicology, that is, "the art and basic science of poisons," and reflecting on how this discipline may have related to earlier armies, one will almost certainly conjure up ideas of assassination attempts and poisonings of troops.[1] Examples of both occured in the United States. One was probably accidental, the other intentional.

In the late 1670s, Nathaniel Bacon led a rebellion against the Colonial Governor in Jamestown. A thousand English troops were sent to suppress the rebels; however, by the time they arrived, Bacon had died of a fever and the Governor was gathering the other insurgents. The troops made camp, stood by while trials and executions were carried out, and foraged for food. One group returned with the foliage from a leafy plant, which they cooked as a mess of greens. What followed was described as "a very pleasant Comedy" performed by "natural fools." Recorded observations included "snearing," "pawing," "kissing," and "nakedness" that lasted 11 days and passed without any of those affected remembering what had occurred. They had consumed the leaves of the thorn apple, *Datura stramonium*, which contains belladona alkaloids. Because of this incident, the thorn apple became known as the Jamestown weed, a name later corrupted to jimson weed.[2]

The second incident was directed at George Washington. Thomas Hickey, a member of Washington's guard and a Tory sympathizer, plotted with the daughter of a New York City tavern keeper to add an unknown poison to Washington's food. The woman apparently had a change of heart and whispered a warning to her guest while serving him peas. The peas were not eaten. Hickey later attempted to form a secret Tory corps within the rebel army and participated in planning for the burning of New York City and the assassination of General Washington by stabbing. Thomas Hickey was hanged on 28 June 1776, distinguishing himself as the first American soldier to be executed.[2]

The art of toxicology also was used very early in history to directly improve the warrior's offensive capability in combat. Arrows with poisoned tips probably appeared on the battlefield before 1500 B.C., since the Ebers papyrus of approximately the same period contains a recipe for aconite, an arrow poison used by the ancient Chinese.[1]

The three episodes above are interesting but provide little insight into why the modern military developed a need for toxicological expertise. Certainly, the potential contamination of food rations with toxins remains an important military concern, and the introduction of toxic chemicals onto the battlefield in the form of poisoned arrows might be considered a harbinger of the chemical warfare of World War I. However, the massive military machines with incredible firepower that began appearing in the latter nineteenth century, and the dispatching of U.S. forces to the far corners of the world, to the depths of the ocean, and beyond the earth's gravity introduced questions about toxic hazards that challenged the most expert toxicologists.

To fully appreciate the importance of the milestones discussed below, one must expand the traditional definition of toxicology to include the contributions made to hazard identification and communication, standards development, and the formulation of policy regarding public health, the workplace, and the general environment. Several significant events are summarized under the categories of chemical warfare, conventional munitions, toxicity of materials, and military enclosed spaces.

Chemical Warfare

Early warriors and military minds of the American Civil War pondered the use of highly effective chemical weapons on the battlefield; however, the world's chemical expertise was undeveloped and could not support the concept. Additionally, the attitude that chemical warfare was repugnant probably existed in antiquity. A Latin quotation, and perhaps the first prohibition against the military use of chemicals, reads: "War shall be waged with weapons, not poisons." This situation began changing in the decades preceding World War I. The European chemical industry experienced extraordinary growth, with Germany emerging as a leader. Basic work on dichloroethylsulfide, which we would later recognize as "mustard," was conducted by the English chemist Guthrie as early as 1860. He described its blistering effect on skin when applied as a liquid. The Swedish chemist Scheele produced chlorine, arsenic, and hydrogen cyanide. By the turn of the century, these chemicals were available in large quantities and military applications were being considered seriously. Concern that these substances might be used in anger prompted nearly all the European states to adopt in 1907 a prohibition against the use of poisons in warfare.[3–5]

Restraint in the use of chemical weapons lasted only 8 years. Germany entered World War I with plans that called for only a few months of intensive warfare. The winter of 1914–1915 brought about serious depletion of ammunition stocks and Germany looked to ways of mobilizing national industries behind its military forces. The French had used tear gas as early as August 1914 and the German chemical industry was very powerful. The choice seemed obvious to everybody except the Allies, who seemed to think it would never happen. On April 22, 1915, at Ypres, Belgium, the Germans launched their first gas attack using chlorine. Attacks with phosgene, mustard, and a number of other agents (including the pulmonary irritant chloropicrin and the vesicants chlorarsine and bromoarsine) followed.[3–5]

The Allied military physicians did not know how to treat gas casualties. The U.S. observed the events occurring in Europe but did not seriously investigate the physiology, pathology, and therapy of chemical warfare injury until 1917, the year we entered the hostilities. When studies were finally initiated, these were directed by the medical and the pharmacology and toxicology sections of the U.S. Army Chemical Warfare Service, in collaboration with the U.S. Bureau of Mines; Yale University; American University; Western Reserve University; and the Royal Engineers' Experimental Station, Porton, England. Considerable work was done that contributed to the development of toxicological methodology. For example, various exposure chambers were designed and built, the strengths and weaknesses of different animal models were studied, and considerable emphasis was placed on finding ways to evaluate pulmonary and ocular toxicity.[5,6]

In World War I, almost 100 thousand people were killed and more than 1 million casualties were inflicted because of the use of poison gas. The 1925 Geneva Protocol banned the use of poison gas but permitted its development, production, and storage. Unfortunately, the use of chemical warfare agents has continued. Italy used it against Ethiopia (1935–1936); Japan used it against the Chinese (1939–1944); and Iraq used it against Iran and against its own Kurdish population (1983–1988). In 1969, President Nixon unilaterally halted the production of chemical weapons in the U.S. This action resulted in large stockpiles of chemical warfare agents that would be left in place, to deteriorate and to eventually create a major waste disposal problem. The 1986 Defense Authorization Act required the destruction (demilitarization) of the aging munitions and agents. In keeping with the U.S. position that a chemical weapons capability deters an enemy poisonous gas attack, the 1986 Act also approved production of a new kind of chemical weapon, the binary system. In the binary system, two components of toxic but sublethal character are manufactured and stored separately. When the weapon (e.g., an artillery shell) is fused, separate containers of each component are installed. On firing, the separate containers rupture and the components mix to reach lethality.[7–10]

Both the planned destruction of old chemical warfare munitions and the production of the binary system created many new questions and issues, and they echoed many old questions and issues about chemical agent toxicity. From the first use of chemical warfare agents in World War I to the present, the U.S. Army has never stopped laboratory work on chemical agents, although the emphasis has changed over time. The concerns that have fueled this research have resulted from the possibility of chemical agent exposure with armed conflict; terrorist activities; the destruction of our aging chemical stockpile; the accidental unearthing of old, forgotten burial sites; and the production of the binary system.[11] Beginning with World War I, the Chemical Warfare Service had both medical and research sections. This arrangement continued until 1979 when the Biomedical Laboratory of the U.S. Army Chemical Systems Laboratory, Edgewood Area of Aberdeen Proving Ground (APG), Maryland, was transferred to the U.S. Army Surgeon General, thereby creating a sharp distinction between Chemical Corps research and U.S. Army Medical Department research into antidotes and the defensive aspects of chemical warfare. The two laboratories that resulted were the Toxicology Division of the U.S. Army Chemical Research, Development and Engineering Center (CRDEC), APG, Maryland, and the U.S. Army Medical Research Institute of Chemical Defense (U.S. AMRICD), which is also at APG.[5,11–13]

Conventional Munitions

It was not until the eleventh century A.D. that propellants and explosives as we know them began to emerge. Using

potassium nitrate (saltpeter), sulfur, and charcoal, the Chinese developed explosives that sometimes burned and sometimes exploded. Their early military use of this material probably included experimentation into propelling objects from bamboo tubes; however, the Arabs were given credit for inventing the first gun in 1304.[14]

Knowledge about the mixture of saltpeter, sulfur, and charcoal, or "black powder," spread throughout the western world between the thirteenth and seventeenth centuries. In the colonies, powder making was initally conducted in a primitive fashion as a small cottage industry. Later, powder mills were constructed, but there were few innovations in the powder industry until the mid-nineteenth century, when a new military explosive called guncotton appeared in America. This nitrated cotton, invented in Switzerland, was far ahead of its time and was rejected by American manufacturers because it was too costly to produce and its strong gases ruined gun barrels. Later, in 1866, Alfred B. Nobel perfected a superior explosive after experimenting with mixtures of nitroglycerin and various materials including black powder, charcoal, brick dust, and wood dust. He named his new explosive dynamite. Dynamite was primarily a commercial explosive because it was extremely effective in breaking up rock and ore and greatly increased production in the mining, excavating, and oil drilling trades. Nevertheless, the rapidly developing dynamite industry demonstrated several features that signaled major changes in the manufacture of military explosives and propellants. These included a relatively safe explosive, affordable cost, and an explosive that could be modified to fit a variety of different applications. As for black powder, the Spanish–American War (1898) was the last major conflict in which it was used in large quantities. Black powder continued to be employed for special applications, e.g., in primers and fuses; however, World War I (1914–1918) was fought with a new generation of explosives.[14]

Prior to World War I, Americans had been heavily reliant on the German chemical industry. The U.S. industrial base contained very little expertise in the production of many of the chemicals needed in wartime. Therefore, the U.S. industries, especially those dealing with coke by-products, had to realign to produce dyes, aniline, and nitric acid, which was critical to the production of munitions. The leaders of these industries expressed concern about preventing explosions but had no interest in the toxicity of industrial chemicals, particularly unfamiliar ones like picric acid and trinitrotoluene (TNT). Dr. Alice Hamilton, the pioneer of American occupational medicine, inspected many munitions plants for the U.S. Department of Labor. She sometimes located the industrial site "by the great clouds of yellow and orange fumes, nitrous gases, which in those days of crude procedure rose to the sky from picric-acid and nitrocellulose plants. It was like the pillar of cloud by day that guided the children of Israel." At other times, "canaries," workers stained yellow with picric acid, led her to the plant.[15]

Both Hamilton and U.S. Army sources documented the morbidity and mortality from occupational diseases that were attributed to exposures in the U.S. munitions industries. Exposure to oxides of nitrogen and TNT were thought to account for most illnesses and deaths due to toxicity. The Army reported that in World War I there were 230 fatalities (presumably due to occupational diseases) per billion pounds of explosives manufactured.[15,16]

Hamilton considered "nitrous fume poisoning" to be an engineering problem that manufacturers eventually corrected. However, TNT poisoning was a different matter. Acccording to Dr. Hamilton, the English knew about the problem of skin absorption with TNT exposure, and English manufacturers paid attention to the need for plant cleanliness and personal hygiene in the workplace, to include having washable working clothes and showers. Manufacturers in the U.S. did not do these things. In England, there was a wealth of clinical information concerning TNT poisoning, but American physicians apparently did not know what to look for, were indifferent, or were secretive.[15]

Alice Hamilton attacked the explosives industry in several ways, including 1) causing the National Research Council to appoint an expert committee to act as a consultative body and 2) working to establish a code to protect TNT workers. The expert committee made it possible for medical students to visit TNT plants and to study exposures and poisonings. Additionally, in April 1919, 5 months after the armistice, a code was published. Unfortunately, the code was voluntary and weaker than the British code.[15]

Dr. Hamilton was a pacifist, but she acknowledged the advancement of industrial hygiene and toxicology in America as a result of World War I: "The war did have a beneficial influence on industrial hygiene. If it increased the dangers in American industry, it also aroused the interest of physicians in industrial poisons. And that interest has never died down, on the contrary it has increased with the increasing complexity of methods of manufacture."[15]

During World War II, in the U.S. munitions industry, 968,000 man-years of operations resulted in 28 occupational disease fatalities (22 from TNT exposure, 3 from oxides of nitrogen, 2 from carbon tetrachloride, and 1 from ethyl ether). These numbers equate to less than three occupational disease fatalities per 100,000 man-years of work or five fatalities per billion pounds of explosives manufactured, a ratio 46 times lower than that observed for World War I.[16]

One significant reason for the large difference in occupational disease morbidity and mortality between World War I and World War II was the establishment of the U.S. Army Industrial Hygiene Laboratory at the Johns Hopkins University School of Public Health, Baltimore, Maryland, in 1942. The laboratory consisted of people skilled in medicine, chemistry, toxicology, industrial hygiene, and engineering. Their mission was to assess occupational health hazards at various industrial facilities supporting the war effort. The

laboratory focused on operations in munitions plants, arsenals, and depots, and the associated toxicological issues were addressed by the military services, the U.S. Public Health Service, and civilian institutions. Literature reviews were done to obtain all existing toxicity data on aromatic amino and nitro compounds, which included most explosives, and extensive field and laboratory research studies examined the toxicity of many different types of explosives, including TNT, pentaerythritoltetranitrate (PETN), and RDX (cyclonite). Additionally, the U.S. Public Health Service evaluated stream pollution from explosives plants.[16,17]

History has demonstrated that military planners and weapons developers will never cease in their search for better and more powerful explosives and propellants. However, history has also shown that human health effects must be determined early and appropriate steps taken to protect those who may encounter toxic exposures. Toxicological work in this area has continued to be addressed by the U.S. Army Environmental Hygiene Agency (U.S. AEHA, formerly the U.S. Army Industrial Hygiene Laboratory), APG, Maryland and the U.S. Army Biomedical Research and Development Laboratory (U.S. ABRDL). U.S. ABRDL was established at Edgewood Arsenal, Maryland, in 1972 as the U.S. Army Medical Environmental Engineering Research Unit. In 1974, it was transferred to Fort Detrick, Maryland, becoming the Environmental Protection Research Division of the U.S. Army Medical Bioengineering Research and Development Laboratory. It was renamed U.S. ABRDL in 1986. In 1978, toxicological research needs exceeded the capabilities of U.S. ABRDL, and toxicology studies were initiated at the Letterman Army Institute of Research (LAIR), Presidio of San Francisco, California. In 1988, the toxicological effort at LAIR was discontinued.[17-21]

Toxicity of Materials

The toxicological issues encountered by the military services in World War II rapidly expanded beyond the munitions industry. This was the result of several factors: 1) following World War I, the U.S. chemical and automotive industries experienced tremendous expansion and became suppliers of an incredibly long list of new materials; 2) the expansion of American industry was accompanied by an awareness of the adverse health effects that may result from exposure to chemicals; and 3) the U.S. military in World War II had more people scattered over a wider geographical area than in any other war in history. Uniformed people were coming in contact with chemical compounds that were intended to keep their machines running, to protect their equipment from mildew, and to protect them from disease-carrying insects and pathogenic agents such as malaria. To help deal with the complex issues of product safety and toxicity, a Toxicology Branch was established in the Office of the Army Surgeon General in January 1944. This Branch worked with numerous laboratories and the U.S. Public Health Service to provide the urgently needed toxicological assessments. Substances that were evaluated included fungicides, flame retardants, fuels, cosmetics, plastics, adhesives, alloys, food stuffs, methyl bromide, DDT, and other insecticides, miticides, and repellents including aerosols. Unfortunately, many opinions on the presence or absence of toxic hazards were rendered on the basis of judgement only because the needed scientific data were not available. The toxicological capability of the uniformed services had been overwhelmed. This unfortunate and unacceptable problem was clearly recorded in the medical archives of World War II.[15,16,22-24]

Following World War II, the U.S. military would retain a global posture, tropical infectious diseases would continue to pose serious threats, and the list of new chemicals used in vehicles, equipment and clothing, and applied directly to the skin would continue to grow unceasingly. The last 45 years have demonstrated time and time again that the questions of acute and chronic toxicity associated with the use of these chemicals and the materials which contain them must not only be asked but also must be addressed long before there is human contact through production and use. Today, this work continues on a routine basis at CRDEC, U.S. AEHA, and U.S. ABRDL. Safeguards have been implemented that now require the review of all new items in the Army supply and equipment systems, including toxicological assessment, prior to the time these items are made available to troops in the field.[13,25,26]

Military Enclosed Spaces

"Military enclosed spaces" refers to the uniquely military environment that is most often found on submarines, in armored gun turrets, inside armored land vehicles, and on military aircraft and spacecraft. These distinctive military environments are similar in many respects but different in others. The adverse health effects experienced by military personnel serving in military enclosed spaces became apparent in the World War I era. These were addressed to some degree in World War II. However, the unique exposures of military enclosed spaces did not receive the emphasis they deserved until the U.S. went into a period of intense weapons modernization in the late twentieth century.[25,27-31]

Naval Contribution

Even before Archimedes described the principles of submersion, Alexander the Great is alleged to have used a submersible vessel at the seige of Tyre in 332 B.C. From the time of Alexander to 1900, inventors made submarines and attempted to power them by hand, by steam, and later, by electric batteries and petrol engines. One was even deployed unsuccessfully by the Americans against the British in the Revolutionary War. In the American Civil War, a Confederate vessel, the H. L. Hunley, became the first submarine

to sink a warship. This was hardly a victory because the Hunley and her crew also went down in the explosion. The torpedos of the Civil War were attached to a long spar or boom in front of the submarine. The only possible chance for success was for the slow submarine to attack a ship at anchor and to hope for the best in getting away before an explosion occurred. By 1900, several innovations were merged to develop the model for the twentieth century submarine. These included a strong metal hull to withstand great pressure, a self-propelled torpedo that could be launched by the submarine, a gasoline engine for power on the surface, and an electric propulsion system that did not require contact with the atmosphere.[32–34]

Initally, undersea craft had to surface frequently to recharge the batteries. In the 1930s, Dutch naval experts developed the snorkel, which allowed the craft to remain submerged for long periods. (One German U-boat stayed submerged for 69 days.) When necessary, a fan pulled in fresh air and the diesel motors were run under the sea. The internal environment of the submarine before the nuclear age was unpleasant. Submariners described foul, stale air that reeked of diesel fuel and other unpleasant odors, and mildew that covered food, clothes, and bunks. During World War II, there were many reports of reduced effectiveness in submarine crews because of what the Navy called "defective habitability." The following are quotes from U.S. Navy World War II reports:

> "Battery compartment of torpedo flooded during attack, emitting chlorine gas into the boat."
>
> "Lack of air conditioning decidedly had a debilitating effect on crew and slowed their reactions."
>
> "Patrol somewhat handicapped by poisoning (carbon tetrachloride) which affected majority of crew over ten day period."

Carbon tetrachloride was used as a cleaning spray for electric motors. When the motors became hot, it volatilized and produced phosgene.[35,36]

The nuclear submarine made its debut in 1955 and brought with it atmospheric control. Oxygen was extracted from seawater and air scrubbers removed contaminants, but the questions and problems of submarine air quality did not go away. In 1988, after an extensive study requested by the U.S. Navy, the Committee on Toxicology of the National Research Council released a 154-page report on submarine air quality that addressed monitoring and health effects in divers who breathed submarine air under hyperbaric conditions. As we have observed in the past, naval weapons developers will continue to modify and to introduce new materials into submarines. It would be absurd to think that submarine air quality will not continue to be a source of concern and questions.[33,37]

The naval organizations of the world also developed enclosed spaces in their surface ships. Significant improvements in surface vessels occurred in the mid-nineteenth century and many innovations appeared in the military hardware of the American Civil War. These included iron-clad ships; large, powerful naval guns; and revolving, armored gun turrets. Improvements in surface war ships continued, and by World War I, combatants were engaging each other in very large, massively armored, and heavily armed battleships that became known as dreadnoughts. Before the start of World War I, the German Navy experienced problems with "nitrous fumes" filling the confined space inside naval gun turrets when the gun breech was opened for reloading. The gunners were overcome by the irritant gas, and for protection, they wore respirators. The gases causing the problem were probably a mixture of nitric oxide (NO) and nitrogen dioxide (NO_2). The protective masks that were used, consistent with the practice of the day, probably contained soda–lime and activated coconut shell charcoal. While wearing the masks, the gunners were alleged to have developed methemoglobinemia, with deaths occurring. Evidently, the masks did not remove NO and may have actually increased the NO content in inspired air through the reduction of NO_2. As a result, beginning in World War I and for a period thereafter, the Germans conducted creative laboratory studies to differentiate the toxic effects of NO and NO_2. This problem was corrected, at least in the U.S. Navy, with technology that emerged in the 1930s. The final result was a compressed-air bore cleaner that evacuated the combustion products in the large gun tubes before the gun breech was opened. However, the presence of NO and NO_2 in military vehicles is still a matter of serious concern, and the toxicities of these two gases are still compared and debated.[34,38–44]

Army Contribution

The tank is the best example of an Army enclosed military space. The tank first appeared on the battlefield in World War I, primarily a product of British ingenuity.[27] William Divall, one of the first tankers to go into battle described the experience in a letter to his sister:

> "The whole crew are at various guns, which break forth in a devastating fire."
>
> "By this time, the fumes from the hundreds of rounds which we have fired, with the heat from the engines and the waste petrol and oil, have made the air quite oppressive and uncomfortable to breathe in. However, those who go down to the land in tanks are accustomed to many strange sensations, which would make an ordinary mortal shudder."[45]

Two other innovations of World War I, an effective, rapidly firing machine gun and warfare chemicals combined with the tank to create dangerous environments filled with carbon monoxide (CO). The CO came from the incomplete combustion of propellant in the machine gun shells. Casualties from CO occurred before and during the war, causing

French military scientists to conduct field studies. Firing the machine gun in a tank with all hatches closed and the motor stopped produced the highest levels of CO.[27]

A commonly used practice for setting up machine gun emplacements on the World War I battlefield created a somewhat different enclosed space that was also extremely hazardous. Machine gunners in a trench, for example, fearing a gas attack, would attempt to use any material available to create an air-tight envelope around themselves and the breech of their machine gun. What they did was to effectively contain the CO in their breathing area. As a result of the CO studies conducted by the French military, the practice of hermetically sealing a machine gun emplacement was forbidden.[27]

World War II brought bigger, more powerful armored fighting vehicles, and the U.S. Army met this challenge by establishing the Armored Medical Research Laboratory at Fort Knox, Kentucky, to deal with the complex issues of this new man–machine interface, including the toxicity of propellant combustion products.[27,30,31] Progress was made in identifying the toxic hazards in World War II armored vehicles, but after the war, the Army Medical Department seemed to forget about this research area.[27] However, questions about armored vehicle habitability did not go away; instead they reached an incredible level of complexity in the early 1980s, as the United States began developing armored fighting vehicles that carried large-bore guns and that were sealed and artificially ventilated so that they could operate on a chemical battlefield. Additionally, these vehicles were to be constructed in such a way that soldiers inside a vehicle that was hit by an enemy shell would have the greatest chance possible of surviving. This meant careful evaluation of the types and quantities of potential toxicants that can be found inside an armored fighting vehicle which has been penetrated by an enemy shell and follow-up of field studies with appropriate bench studies. Considerable work has been done within the Army and under contract, including studies of CO and the oxides of nitrogen. This has been accomplished by the Walter Reed Army Institute of Research, Washington, DC, with certain aspects being addressed by the U.S.ABRDL, Fort Detrick, Maryland, and the U.S.AEHA, APG, Maryland. Vehicles, equipment, and soldiers in the recent Persian Gulf War benefited from these efforts, which are continuing.[25,27,28,30,31,43,44]

Air Force Contribution

Unlike the other services, the U.S. Air Force avoided serious problems very early in the rapid development of air and space technology. In the period between World War I and World War II, military aviators were already looking beyond the stratosphere. However, the physical stressors and oxygen requirements of high-altitude flight forced the early development of the enclosed cockpit or cabin with pressure, temperature, and oxygen control. In most cases, this development shielded the aviator from the toxic hazards of combustion products, fuels and lubricants, aircraft cleaning materials, and anti-icing agents. Nevertheless, a whole host of ground support personnel still faced these hazards; environmental problems, e.g., fuel spills, still occurred; and toxicological assessments remained critical components of accident investigations. In the case of cargo or special function aircraft, the cockpit or cabin did not always afford a high degree of protection from exposure. The best known example of this is the exposure of Operation Ranch Hand personnel to Herbicide Orange (with its dioxin contaminant) in Vietnam. As we enter the era of extended space flight and space stations, the U.S. Air Force may write a new chapter on enclosed military spaces, or perhaps they may only add to the saga started by the submariners.[46–48]

The Future of Military Toxicology

I believe that military toxicology is a distinctly different discipline. It plays a major role in the toxicological assessment of health and environmental hazards associated with substances that are used primarily by the military or that present as an unusual type of exposure as a result of a unique military environment.

What does the future hold for military toxicology? There will continue to be a high level of activity related to the environment because of public concern and significant legislation, and great pressure will be brought to bear to find alternatives to our current animal models. Additionally, there will be increased collaboration and cooperation between the military services in conducting toxicological assessments. However, for the most part, military planners and developers will continue to develop new materials and weapons to gain the advantage, just as they have done since the beginning of time. The problems and issues that I have presented and that have kept us busy since World War II will continue.[13,49,50]

In struggling with many of the programs and problems I have discussed and in preparing this report, I found that military toxicologists are generally not very interested in history nor do they make a great enough effort to preserve their work for posterity. Therefore, I ask you to take the time on a routine basis to ensure that your work will always be accessible in established archives; it will be needed again at some time in the future. Please keep in mind the words of George Santayana, "Those who cannot remember the past are condemned to repeat it."

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Historical Aspects of the Development of Quantitative Risk Assessment Technology in the U.S. Navy

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The history of the toxicology programs of the military services is an appropriate consideration when addressing the application of science, policy, and practice to chemical risk assessment in the Department of Defense. Assessment of risk implies evaluating the probability of adverse effects caused by a chemical — under specific conditions — as opposed to a more straightforward description of the toxicity (potential for harm) of that chemical.

History, however, is much more than a chronological listing of dates, times, and places. Rather, history is a chronicle of interactions and influences and is sensitive to interpretation in the context of time. The history of any scientific endeavor must, therefore, be interpreted in the context of an often ill-defined and constantly changing entity — "state of the art." The very nature of a scientific program and the military facility that has the mission of carrying out the program cannot be treated as a tale of an inanimate object, but it must be recognized as being the product of individuals who manned the laboratory, the goals to which they aspired, and the conditions and constraints under which they worked.

Toxicology — Art or Science?

It has been said that toxicology is the oldest of arts and the newest of sciences. At some time, however, a demarcation or transition from one (the art) to the other (the science) occurred and a recognizable shift from mostly art to predominantly science became evident. It is usually not possible to pinpoint a precise date and time when such a transition occurs. In fact, that transition may only be apparent when examined some years later and only be visible through the "retrospectroscope" (and with a rose-colored lens, at that). The very real exponential growth of the toxicology profession (including the advent of "instant toxicology") spanning the decades of the 1960s and 1970s lends considerable support to the notion that practitioners of toxicology in those years not only witnessed but contributed to the transition from art to science. It was not merely coincidence or happenstance that the concept of quantitative risk assessment emerged at about the same time. The constantly and rapidly changing profession of toxicology as well as the rapidity of growth contributed to (or caused) the alternating precision and fuzziness in the definitions of "state of the art." The history of the toxicology programs of the uniformed services transcends this time of change in the profession of toxicology and was shaped by and helped shape the entire profession.

Continuing the notion of a mix between art and science, most toxicologists are not even trained as toxicologists. It is difficult to define precisely what toxicology really is. Perhaps, it is a mind-set. Certainly, it is not a basic science. The significant advances in what we usually consider to be "toxicology" are really advances in biochemistry, pathology, physiology, etc., and are usually closely related to the advancement of "state of the art" (that phrase again) in analytical chemistry. Because toxicology is such an applied endeavor, it follows that applications of those advances of our colleagues in the basic sciences are what occupy the toxicologist; as, for example, in the process of chemical risk assessment. Much of what we usually consider to be toxicology is intertwined with the use of new knowledge and techniques to define the biological actions of chemicals on humans, to quantify dose–response relationships between those chemicals and effects, and to predict exposure conditions that will not be harmful to human health. Evidence of this can be seen in the variety of educational backgrounds of investigators who have contributed to the U.S. Navy's toxicology program: biochemistry, biochemical kinetics, physiology, pharmacology, clinical chemistry, psychology, pharmacy, zoology, chemistry, and toxicology.

The Early Years and A Need for a Program

During the decade of the 1950s, it became apparent that the Navy would be encountering toxicology problems that would require a significant expenditure of resources to solve. Weapons systems were becoming increasingly complex and the general awareness of health hazards (and ensuing mission degradation) resulted in the formation of the Navy Toxicology Unit (NTU).

The Navy Toxicology Unit

The Navy, in common with its sister services, can trace

the beginnings of "military toxicology" to the questions that required answers during the World Wars. There was, however, no permanence associated with the organizational subunits which provided that toxicology support. The real roots of the Navy's toxicology program coincide with the foresight and vision of Captain Jac Siegel which resulted in the establishment of the NTU. Captain Siegel conceived the notion of a dedicated unit that would be responsive to the requirements of the "customer." Captain Jack Kinsey was part of the Deep Submergence Systems Project Office that had the responsibility, in consonance with the Bureau of Medicine and Surgery, for solving man/machine interface problems concerned with nuclear submarine habitability. Rear Admiral Bart Hogan, the Navy's Surgeon General, appreciated the magnitude of the problem and realized that the formation of a dedicated unit, as proposed by Captain Siegel, was the best means of solving it. NTU started operations using 3000 square feet in Building 119 at the National Naval Medical Center (NNMC) in Bethesda, Maryland, in 1958.

The Original Mission

The reasons for the formation of NTU have a great deal of historical significance. The scope of the Navy's program expanded markedly during the decades of the 1960s and 1970s. Those were the toxicology "boom years." Significantly, the philosophy behind the program and, therefore, the mission have changed little. Of interest are the definitions of mission and function that were assigned to NTU and, therefore, to the Navy's toxicology program:[1]

> "...To provide technical and specialized services in the fields of operational toxicology and health engineering as related to toxicity problems encountered aboard ships; and in the design and use of new weapons systems. Also, develop and provide biological data so that precautionary measures, conducive to good health practices, may be prescribed."

Even in the context of the terminology and jargon of three decades later, some of the terms, to a large degree, sound like what is now considered to be risk assessment:

- "Operational toxicology" carries the connotation of defining risk.
- "Health engineering" implies mitigation of risk.
- "Precautionary measures, conducive to good health practices" infers management of risk.

Continuous Exposures

Experimental data were required to establish safe exposure limits for continuous exposures. Because we are considering the historical aspects of toxicology, it is appropriate to cite the origin of several commonly accepted parts of toxicology experimentation. At the time of the formation of NTU (actually one of the reasons for its establishment), no laboratory was prepared to do 24-hour/day animal exposures. The original NTU modified the existing design Rochester Chambers for the first big push toward continuous exposure studies.[2,3] Today's continuous exposure equipment has little resemblance to those crude beginnings. It is usually not possible to pinpoint the beginning of some things. For some reason, 90-day studies have become an accepted norm. There is considerable support for the notion that standardizing on this time period was an outgrowth of a planning meeting of the NTU staff in Captain Siegel's office. In order to standardize protocols, it was decided to add a 50% margin to the published figure of 60 days for the duration of nuclear submarine patrols and, thereafter, exposures of experimental animals would be for a duration of 90 days.

There are still concerns about continuous exposures in operational environments. In documents written to solicit proposals for their Centers of Research and Training, the National Aeronautics and Space Administration (NASA) considered that, toxicologically, the closest thing on earth to a space station was a nuclear submarine.

Operational Toxicology

The concept of operational toxicology is an important part of the Navy's toxicology program, but it is by no means limited to the Navy. Military toxicology research is structured and administered in consonance with the rest of the Department of Defense (DoD) research. Because appropriate toxicology data for risk assessment purposes are almost never available, it is often necessary to first develop technology as part of developing specific data — the technology by which risk assessment is accomplished.

Risk Assessment

To the extent that risk assessment includes evaluation of toxicity under a given set of exposure criteria, the Navy's toxicology program has always been risk oriented. To accomplish the end of protecting the health of military personnel and enhancing mission performance, there is no way of freezing a toxicology research program into standard protocols that only define toxicity. Hazard assessment (toxicology under conditions of exposure) has always been part of the Navy's program as the original mission and function statement dictates. Chemicals that are encountered in the design and use of most weapons systems are, for the most part, new and (very frequently) "reactive." It is seldom possible to consult the scientific literature and find sufficient toxicologic data on such chemicals on which to base a risk assessment. New information must be developed.

The Military Mission and Acceptable Risk

Of necessity, much of the practice of military toxicology was (and is) directed toward the requirement for the absolute

infallibility of the military mission when called. There is no room for occupational health episodes that adversely affect mission performance. In today's language, this concept is identical to the process of identifying the degree of "acceptable" risk. In the context of acceptable risk as regards mission-sensitive occupational health hazards of military weapons systems, the amount of risk that is acceptable is very close to zero. Because of this extremely low degree of acceptable risk, any experimental studies upon which human exposure limits are to be based must be proficiently (if not elegantly) done. The academic freedom under which most Navy toxicologic experimentation was (and is) done is usually astonishing to those unfamiliar with the military programs. In common with much of the rest of DoD research, "worst case" scenarios are considered in experimental design. Interactions with the environment, including physiological adaptations, constitute an integral part of the program. Modern approaches to extrapolation, or "scale-up," were (and are) integral to Navy toxicology. There is a strong mission orientation that can be directly attributed to the fact that the program is done in a "user laboratory" which has the goal of protecting the health of the users — Navy personnel.

Nuclear Submarine Habitability

When the Navy was well into the development of the nuclear submarine, there was a very real concern for the establishment of human exposure limits for chemicals when exposure was to be on a continuous basis. This was the first problem to which the resources of NTU were directed. (The magnitude and significance of this problem is shown by the fact that some 30 years later nuclear submarine habitability is still an important concern of the Navy Toxicology Detachment.) In the realm of occupational toxicology, Threshold Limit Values (TLVs, 8 hours/day for a working lifetime), developed by the American Conference of Governmental Industrial Hygienists, had been around for some time. The nuclear submarine was the first time that it was necessary to protect man in an occupational environment which, in effect, brought man into equilibrium with the environment and then held him there for a prolonged period of time. There was only one "loading," at the beginning of the cruise and one "unloading," which occurred at the end. What was the relationship of the required exposure limits to TLVs? Would it be safe to take existing TLVs and make a correction for exposure (divide by 24/8, or 3)? What was the best way of establishing exposure limits? No one really knew the answers.[4]

It is more than just passing coincidence that the scientific meeting which first addressed these major concerns was, in fact, the first in a long series of meetings addressing the military's concern about environmental and occupational toxicology. This present conference is a direct lineal descendent.

Military Operating Environment

Military toxicology has developed into something that is intertwined with awareness and concern for operational environments and theaters. There is consideration for the interaction of abnormal physical environments (and the physiological adaptations thereto) with chemical toxicity, both for esoteric military chemicals and for such items as carbon monoxide that toxicologists have been studying for years.[5] There is very real concern for the effect of even very slight performance decrements on mission performance, when that mission involves operation of high-performance aircraft or pressurized, undersea vehicles with complex electronic weapons systems.[6] As one thinks these out, they become increasingly complex. What about a fire on board an aircraft carrier conducting flight operations in a combat situation? Because of threat scenarios involved in conflagrations as well as other catastrophic exposures, rate of onset of toxicity is an important concern.[7] And there are more!

The Need for Quantitative Toxicology

As part of normal program growth, and in consonance with changing philosophies in toxicology that have been discussed, the Navy's toxicology program became progressively more and more oriented toward the understanding of mechanisms of action for those toxicants with which it was concerned.

When assessing risk, it is necessary to quantify as much as possible. Common risk assessment procedure begins with studies of effects on experimental animals. Dose–response data thus obtained are "scaled-up" to human scenarios.[8] In practice, because this species-to-species extrapolation is inexact, "safety (ignorance?) factors" are employed. The magnitude of the safety factor is determined by several things, including severity (and reversibility) of effect whose risk is being assessed, known interspecies variation, and, importantly, the quality of the experimental data on which the whole procedure is predicated.

Physiological Factors Affecting Toxicity

The Navy was once faced with the need to establish a continuous exposure limit for 1,1-dichloroethylene (vinylidene chloride, VC). The need was complicated by the fact that little of practical consequence could be done to alleviate the exposure and that there was a paucity of experimental data on VC toxicity.[9] Application of appropriate safety factors would result in an operationally unacceptable (low) and unrealistic exposure limit.

Two simultaneous programs evolved. The obvious need for appropriate experimental data was addressed immediately with a series of studies designed to define and quantify the mechanistic toxicology of VC in experimental animals. Emphasis was placed on early detection of VC-induced alterations through biochemical means.[10–12] The intent was to

provide information on early detection of toxicity as well as on thresholds of impairment and damage.

In addition, the extrapolation issue (with its necessarily large safety factors) had to be considered. Despite vast differences in size, there is a remarkable degree of physiological constancy between and among mammals.[13] Whatever the species, a toxic response is the result of a dose that has been delivered to a site of action. The processes of uptake, absorption, distribution, metabolism, and elimination are dynamic ones. The size of the delivered dose is variable and is determined by a variety of physical and physiological factors, which can be modeled.[14,15] In addition to physical factors (e.g., solubility, partitioning, etc.)[16] that are determinants of uptake, a variety of physiological factors (including blood flow and perfusion) are determinants of distribution.[17] To the extent that the dose is related to these and other physiological factors, physiological differences among species in those parameters are an important part of the scale-up, or extrapolation.[18] Knowledge of, and inclusion of, these factors and the development of appropriate models to test them, paired with appropriate and good quality experimental data, can, indeed, minimize the magnitude of the ignorance factor.[19]

Naval Medical Research Institute Toxicology Detachment

In the middle of the 1970s, NTU was disestablished and its personnel and other assets were reassigned as the Toxicology Division of the Environmental Biosciences Department of the Naval Medical Research Institute (NMRI). As the Navy's toxicology program grew and became more oriented toward mechanistic toxicology during the 1960s and 1970s, the original 3000 square feet in Building 119 at NNMC became progressively more restrictive. The mechanisms work, which was a necessary part of the growing need for quantitative toxicology, could not supplant the studies intended to provide descriptive toxicity data. There was a continuing requirement for both types of research. Part of this increased program was, of course, related to increased awareness of the toxic hazards of chemicals on the part of the general public which was occurring during this time period. Program growth could not be supported by physical facilities that were scheduled to come on line at Bethesda.

Two historically significant events occurred. The toxicology program of the U.S. Air Force included a significant portion of effort that was supported by an in-house contractor at the Aerospace Medical Research Laboratory (AMRL) at Wright–Patterson Air Force Base. Fortunately, a significant portion of this contractor's time was available because Building 119 was found to have termites! There was little question about the potential for adverse effects on NTU's experimental animals that could be caused by the use of a persistent organochlorine termiticide in Building 119. The die was cast!

After preliminary (and very amicable) meetings, it was agreed that both services would benefit by co-location and cross-utilization. It was felt that the technical specialties of each of the services and their program goals would complement each other. It was proposed and agreed that NMRI would co-locate its toxicology program with the Air Force's program at AMRL and, in order to accomplish this, would establish a detachment (which was essentially the old NTU) at Wright–Patterson Air Force Base. Through this mechanism, the Navy could cross-utilize a significant portion of the Air Force's contract and (simultaneously) continue its development of quantitative risk assessment. This relationship has proved beneficial to both programs and may provide the blueprint for other joint-service research projects and programs.

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History of Air Force Toxicology

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The U.S. Air Force Toxicology Program traces its beginning to the early 1950s with the hiring of Dr. Anthony A. Thomas. He assembled a staff consisting of a medical technologist, a pharmacologist, and a veterinary pathologist in the basement of the Wright–Patterson Air Force Base Area B hospital dispensary. Studies were initiated on the occupational toxicology of missile propellants and oxidizers. As the program grew in productivity and importance, it was moved to its present location in Building 79. There, four inhalation toxicology chambers with hypobaric, continuous exposure capability were constructed. They were named the "Thomas Domes" after the originator of the design. These original and four additional domes served as the "backbone" for inhalation studies on oxygen-enriched atmospheres, the hydrazine propellants, carbon monoxide, and a number of other compounds of interest to the Navy, Air Force, and the National Aeronautics and Space Administration during the 1960s and 1970s. This paper traces Air Force toxicology through the era of continuous inhalation exposure into inhalation carcinogenicity exposure and finally to the development of physiologically based, pharmacokinetic modeling.

The Beginning

The first documented reference to a toxicology effort in the Aero Medical Laboratory at Wright–Patterson Air Force Base (WPAFB) is found in *50 Years of Research on Man in Flight*.[1] Major Edward Westlake developed an industrial hygiene program for missile bases to ease military and civilian concern about the new rocket propellants' toxic properties. Surveys were conducted of potential hazards and handling procedures and preventive remedial measures were formulated.

It is generally accepted that the beginning of the Air Force research toxicology program as we know it today at WPAFB originated with the hiring of Dr. Anthony A. Thomas as a research toxicologist in 1956. He was assigned space in the basement of the WPAFB Dispensary in Area B. By 1960, he had assembled a staff consisting of Mildred Pinkerton, a medical technologist; Dr. James Prine, a veterinary pathologist; and Dr. Kenneth Back, a pharmacologist, who was later to become a Branch Chief and a major, long-term contributor to the program. They set about the complex task of defining the toxicology of Air Force missile propellants and related components to respond to some of the concerns raised by Major Westlake's industrial hygiene surveys. From this relatively inauspicious beginning was to emerge an inhalation toxicology program and one-of-a-kind supporting facility that would gain national recognition for excellence within the next decade.

Growth and Maturity of the Program

The Aeromedical Laboratory became the Aerospace Medical Laboratory in 1959. It had been designated as the fundamental focal point of the new Air Force initiative entitled Man in Space in 1958. The design of ecological systems to support extended space travel required human exposure limits for a wide range of environmental contaminants present in space cabins. The only toxicologic data available were directed at the 8-hour/day, 40-hour/week occupational exposure. The need to extend this data bank to the 24-hours/day, 7 days/week continuous exposure for extended periods was obvious. The U.S. Navy was encountering similar requirements as it examined the prolonged submergence of Naval personnel in nuclear submarines. The Naval Medical Laboratory hosted a Symposium on Submarine and Space Medicine in 1958 as an initial thrust to address these problems.

Dr. Thomas recognized that a facility to perform continuous exposure toxicology studies was essential to meet these needs. Because no such facility existed to fulfill these needs, he set about the task of designing and constructing such a facility. In 1962, the toxicology program moved from its basement quarters in the dispensary to Building 79, its present location today. In 1964, four inhalation exposure chambers capable of continuous, uninterrupted exposure under hypobaric and oxygen-enriched atmospheres became operational. These chambers became known as the "Thomas Domes" named after the designer, Dr. Anthony A. Thomas. This facility, which was soon expanded to a total of eight chambers, served as the "backbone" of inhalation exposure studies on the toxicology of a number of atmospheric contaminants for two decades. The final recognition of the maturity of this program came with the establishment of the Toxic Hazards Division as one of the four major divisions of the 6570th Aerospace Medical Research Laboratories in 1965.

During this period of the 1960s, studies to further define the toxicology of the hydrazine missile propellants (hydrazine, monomethylhydrazine, and 1,2-dimethylhydrazine), borane fuels, inorganic fluorine oxidizing agents, and organic nitrogen fluorine-containing compounds were intensified. A number of 90-day, continuous inhalation studies were completed. In addition to the inhalation pathotoxicology of these compounds, studies on the biochemical mechanism of action and possible therapeutic intervention of toxic exposures were instituted. Studies on the cardiovascular and behavioral effects to crew members of halogenated fire extinguishing agents were undertaken because of their projected use in both aircraft and spacecraft cabins. Short-term inhalation exposure studies to develop Emergency Exposure Limits for Air Force personnel working in critical operational environments were performed. Improved analytical methods for detection of these compounds in the operational environment were developed.

The problem of long-term, continuous exposure to oxygen-enriched atmospheres was confronted. Inhalation studies at 100% oxygen at reduced atmospheric pressure corresponding to the early spacecraft cabin conditions were undertaken. Morphometric methodology to evaluate quantitatively the degree of pulmonary membrane thickening characteristic of oxygen toxicity was developed and utilized in these studies. The alteration of the toxic response of atmospheric contaminants in the presence of increased oxygen concentrations was evaluated. A critical evaluation of continuous exposure to the ever present, atmospheric contaminant carbon monoxide was completed. Included in these studies was a study to clarify the effect of carbon monoxide on normal sleep patterns. The renal toxicity from inhalation exposure to saturated concentrations of ethylene glycol was determined for the National Aeronautics and Space Administration (NASA). This was necessitated by the possibility of a leak of this coolant into the spacecraft cabin.

During this exciting time, another significant development occurred. The need for a forum to review progress critically and to exchange information in the rapidly expanding area of atmospheric contaminants in confined spaces became evident. In 1965, a Conference on Atmospheric Contamination in Confined Spaces, sponsored by the Air Force, was held in Dayton, Ohio. It is appropriate to quote from the "Introduction" to the Proceedings[2] of this conference:

> "As our research methods and techniques in toxicology progressed to the point where truly uninterrupted, long-term, continuous exposures became feasible, many new technical difficulties were discovered, and the costliness of this work became apparent. The need for a scientific meeting dedicated primarily to research problems in toxicology became increasingly urgent. Because the number of facilities available to conduct such work is limited in the free world, it has also become critically important that researchers in these facilities should produce data that are directly comparable. This would prevent unnecessary or costly duplication of experiments and loss of valuable biological lead time. Although everyone abhors 'standardization' in research and finds it stifling of initiative, inevitably methodology must be standardized in the sense that only acceptable methods that can furnish reproducible and meaningful information should be used. Thus, the setting of a sort of minimum criteria for research methodology becomes, in fact, a sort of quality control procedure, a highly desirable situation in any research endeavor.
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> "Obviously, this meeting was not intended in any way to become a symposium. The issues at hand required a very practical approach to many matters of technical detail, and the guiding thought was one of trade-off between optimum experimental design and minimum requirements for comparability of data. To provide timely and useful toxicological information to the design engineers one must also compromise some of the goals which the ultimate perfectionist seeks. This compromise then is necessitated by two crucial and overriding factors, available time and money. Therefore, we felt that a conference which provided a workshop atmosphere was much more desirable than would be the highly academic approach of a formal symposium.
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> "We sincerely hope as experience grows and as research data accumulate that there will be a gradual tendency in this series of conferences toward the makings of a real symposium. Meanwhile, I must take the blame for arranging the technical program for this very first conference."

The hopes of the author of this introduction, Dr. Anthony A. Thomas, then the Director of the Toxic Hazards Division, were certainly fulfilled as seen by the successful annual conferences held thereafter.

The Response to Regulatory Pressure

With extended space flight a successful reality, the 1970s brought other pressures to bear on the Air Force Toxicology Program. The need for data to establish permissible exposure limits for chemicals in the workplace became pressing. The hazards associated with exposure to chemicals with carcinogenic potential became an overriding issue. The close structural relationship of the hydrazine propellants to the carcinogenic nitrosamines necessitated definitive data to determine the hazard associated with the continued use of these propellants. Six-month to one-year exposures of mice, rats, hamsters, and dogs to graded concentrations of hydrazine, unsymmetrical dimethylhydrazine, and monomethylhydrazine were conducted. The complete histological

work-up involved the evaluation of over 300,000 tissues according to a protocol designed by the National Cancer Institute. Both national and international corporations involved in the manufacture and use of these compounds provided support for these studies.

Legislative, mandated Environmental Impact Assessments and Statements focused on the need for data to determine the effect of Air Force operations on the environment. A major study on the effect of Space Shuttle exhaust products on the flora and fauna in the vicinity of Vandenberg Air Force Base was undertaken. Test batteries for determining the effect of chemicals on water quality were established. The program responded to the presence of women on the flight-line by adding the evaluation of chemicals on the unborn fetus to its capabilities.

The Navy Medical Research Institute established a toxicology detachment at WPAFB in 1976. Joint Navy/Air Force toxicology studies on jet fuels and hydraulic fluids were initiated. These included studies on proposed alternate fuels derived from such sources as oil shale.

Program Transition

The rapid growth of toxicology as a discipline during the 1960s and 1970s had produced extensive data on the toxicity of chemicals using animal models. There was growing concern among toxicologists about the methodology used to extrapolate animal data to human exposure limits. Under the direction of Dr. Melvin Andersen, the toxicology program initiated a major effort in physiologically based pharmacokinetic modeling. This methodology provides a more exact estimate of the relationship between external and internal dose allowing for species differences in metabolism and distribution of chemical substances. The widespread acceptance of this methodology by the scientific community for use in hazard estimation and risk assessment once again focused the attention on the Toxic Hazards Division as a leader in innovative concepts for toxicologic research. The laboratory has also embarked on a program of developing and evaluating isolated cell systems for use in their research program. This is not, as some may perceive, a result of animal rights pressure but is part of an ongoing effort in the thirty or more years that this program has been in existence to provide the very best in scientific methodology to allow chemicals to be used with minimum adverse effects on employee, community, and environmental health.

With a contingent of the Army moving to Dayton to take part in the program, all three services are now active participants. I have heard Dr. Thomas and Dr. Back discuss many times the desirability of a "Purple Suit"* toxicology program that is Department of Defensewide, that would address the problems of all services because of their similar needs and requirements. One can only wonder if this may indeed become a reality.

*"Purple Suit" is a term coined to denote a military component composed of members of the U.S. Navy, Army, and Air Force but answering to no single service — a tri-service unit.

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Luncheon Address

The Risk of Risk Assessment

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Dr. Falk is the Director of the Division of Environmental Hazardous and Health Effects at the Center for Disease Control. He is noted for his work in several areas dealing with risk assessment, specifically epidemiologic studies and monitoring populations, examining issues of public health and impacts, and dealing with health effects in populations where there is a public health problem throughout the United States. Most recently, Dr. Falk has been involved with a study on lead toxicity in sensitive populations in collaboration with researchers at the National Academy of Sciences.

I approached this address with some trepidation. I am actually here speaking for Dr. Vernon Houk of the Center for Environmental Health and Injury Control at the Centers for Disease Control (CDC) who was originally invited and agreed to give the luncheon address. Unfortunately, he could not be here in person.

For those of you who do not know Dr. Houk, he is a rugged individualist, who has very strongly held views particularly in the area of risk assessment. It is totally in character for him to discuss the "Risk of Risk Assessment" at a symposium on risk assessment. My plan is to present his prepared talk as closely as I can, although I am sure it will lose a great deal of zest and flavor in my presenting it.

By way of introduction, a key issue in relation to the title, "The Risk of Risk Assessment," is "so what is the alternative?" Dr. Houk is very supportive of the approach and he considers it a very important tool. This is not the issue. From a public health point of view, the concern is the uncritical use of risk assessment numbers, the likelihood that we will act upon what are really very uncertain numbers as if they were revealed truths. The "Risk of Risk Assessment" is in a sense a cautionary tale, exemplified by Dr. Houk in what is about as far-fetched and extreme an example of a risk assessment as you might come across. Dr. Houk stated that the average annual rainfall in the United States is 16 thousand inches per year. He had examined the most sensitive population which was Alvin, Texas, and they had 45 inches of rain in a single day a year or so ago. He applied the Alvin, Texas, figure nationally and then extrapolated that to a whole year. The figures showed the cataclysmic rainfall for the entire country. Obviously, this is a serious error and anyone would recognize it as such. The important point is why do we recognize it as such. We have an experiential base which says to us that this is an extreme estimate. We all have lived through rainfalls; we know that 45 inches is an incredible amount for a single day. We know that what may be true for Alvin, Texas, is not true for the state of Nevada. We know that what might happen in one day is not going to last for a whole year. We have some base of knowledge that tells us that this is a very interesting calculation, but it is irrelevant and off by several orders of magnitude.

John Bailar said none of us have the answers at low doses. That is true, but I think the point really is to look at the data. We need to pull together whatever experience and scientific judgement base we have. We need to look at the overall experience, we need to evaluate it, and we need to examine the arrived at numbers. Do the numbers fit or not with what we know, and how are we going to use that information in terms of practical public health experience? To a certain extent, as Dale Hattis said, we can calculate the uncertainty. The data about rainfall is voluminous, and we could calculate the uncertainties in that example to see just how far off we are. However, there are many areas where we do not have the data to actually do calculations; consequently, we must rely on the broad base of knowledge that we have for the area.

When this knowledge base is examined, interesting things happen. Dr. Gold mentioned that there is an incredible difference between how we deal with risk assessment numbers in the environmental and occupational worlds. For example, a number of years ago, we were involved in the evaluation of a landfill, where methane gas and vinyl chloride monomer were dissecting underground to offsite locations and coming up pipes into people's bathrooms. The methane level was high enough to present a risk of explosion, which would have been reason enough to evacuate the homes affected. The health department, however, concentrated its efforts on the vinyl chloride monomer because it was a carcinogen. They measured vinyl chloride levels of approximately 30 or 40 ppb in air collected under the bathroom sink. Now, having done a risk assessment, these proportions turned out to be enough of a carcinogenic risk that there was some serious talk about possibly moving people out of their homes

short term because of the carcinogenic risk. These concentrations are about 1/30 of the occupational level at which we say it is safe to work for a lifetime, even if that is 50 or 60 years. The juxtaposition of the two (whether you are a public health practitioner or just a member of the public) is incredible, that within the same world and in the same community one could think of telling workers that these levels are fine and safe for the rest of their careers, but telling people in the general population that they have to move out of their houses because they are "sensitive individuals."

This is where the risk of risk assessment comes in. The issue is there are many uncertainties. We cannot just apply a model, provide an answer, and have everyone go about their business. We need to examine the hypothesis and the situation; we need to know how to apply this, and even though we have numbers and answers, we need to understand what to do with them. The process of risk assessment is somewhere between an art and a science. Dr. Houk's analogy is that of individuals and their stock brokers. One would prefer to have a stock broker who has a great amount of financial data, who knows how to deal with all the macroeconomic and company data, and who can give you a very detailed answer about what to do. On the other hand, there are not many of us who would believe that the broker's answer is necessarily 100% correct. We have to use the information as best we can and recognize the limitations.

The risk assessment process is distinct from the risk management process. Risk management is the process of integrating the risk assessment results with a variety of other information (e.g., engineering data, socioeconomic and political concerns, and such), weighing the alternatives, and selecting the most appropriate health action, ranging from public education to interdiction or so on. I worry that, at times, the risk assessment process bends a bit towards the risk management process. For example, when one examines how different agencies conduct this process in different settings (e.g,. environmental–occupational), I wonder whether the ways in which we do the risk assessment, in a sense, anticipate the environment in which it is done and the way in which it will be used.

From a public health perspective, and looking at this practically, there are various aspects of the process. We identify the hazards that pose risk to public health and well-being, and we need to manage the risks associated with the hazards prudently and in accord with the public's need. There are a variety of factors that impinge upon us. We need to acknowledge the public's participation; that is essential. We need to communicate the risk succinctly to both experts and laypersons. We need to use information that makes it possible to arrive at an informed estimate of risk. In managing each significant risk, we need to consider alternative actions for controlling the hazards, and we need to advance the risk assessment and risk management process by research to provide information that reduces uncertainty.

As currently done, the final product of risk assessment may often produce numbers that have the illusion of precision; in fact, the process involves many uncertainties. The risk assessment includes judgmental decisions, and each decision is usually made on the conservative side. The end result is a product with many conservative judgments and is, therefore, an estimate of risk that provides maximum protection to the public health. The risk manager or decision-maker must understand the uncertainties that underlie these assessments. John Bailar used the word "conservative" and juxtaposed it with the word "liberal." Dr. Houk uses conservative and juxtaposes it with the word radical. Now, why does he do that? When I started my career at the Centers for Disease Control, we were investigating vinyl chloride-induced angiosarcomas of the liver. I saw the very first cases at the particular chemical polymerization plant where they were found. This led to emergency evaluations by the National Institute for Occupational Safety and Health and the Occupational Safety and Health Administration. This resulted in a quick reduction of the allowable dose in an emergency standard. There was a great concern that this industry would not survive; however, it did.

It can be said that the standards will drive the technology, and people will react if the product is important. Americans and others will figure out new ways to make products. On the other hand, this is a different world than it was in 1973 and 1974. We now face large remediation expenditures based on risk assessment decisions, for example, the Superfund with its billions of dollars and the staggering amounts needed to clean up various sites at the Department of Defense, Department of Energy, and so on. At some point, the government's money will run out. It is not inappropriate at this stage of our country's life to think about weighing the alternatives for how money is spent. Money spent on cleanup driven by the risk assessment process may not be available for other public health uses. If a billion dollars is spent cleaning up mining areas in Idaho and Montana, that money may not be available for preventing millions of cases of lead poisoning in Boston, New York, Chicago, and elsewhere. These tradeoffs will be very real from the public health point of view. We need to examine the costs that are driven by the risk assessment process, and we need to develop alternative ways of using risk assessments.

Risk assessors should clearly define the differences between the elements that go into the process such as scientific fact, consensus assumption, and science policy. The definition of science policy is the Agency's decision on how to handle controversial issues. As one goes down this list, the degree of certainty decreases and in most instances, scientific fact, the element with the most certainty, is the least available to us.

The following are nine commonly used concensus assumptions:

1. When human data are not adequate, adverse effects in experimental animals are regarded as indicative of adverse effects in humans.
2. Results obtained with dose–response models can be extrapolated outside the range of experimental observations to yield estimates or estimated upper bounds of low-dose risk.
3. When an appropriate standardized dosage scale is used, the observed experimental results can be extrapolated across species.
4. There is no threshold for the production of cancer, but threshold effects may apply for other toxicological outcomes.
5. When dose rates are not constant, average doses give a reasonable measure of exposure.
6. In the absence of pharmacokinetic data, the effect or target dose is assumed to be proportional to the administered dose.
7. Risks from many exposures and from many sources of exposure to the same chemical are usually assumed to be additive.
8. In the absence of evidence to the contrary and regardless of the route of exposure, 100% absorption across species is assumed.
9. Results associated with a specific route of exposure are potentially relevant for other routes of exposure.

These assumptions are used and ultimately need to be validated. We cannot go on forever calling them conservative assumptions because, ultimately, we have to live with them for a long time. We must strive to learn how far and in what direction these assumptions differ from the truth. This a very critical part of future needs. Any risk assessment deals with many more assumptions and uncertainties than the nine listed, and this must be emphasized as much as possible.

Another critical area is the evaluation of the scientific study, whether it is epidemiologic or toxicologic. In working with risk assessment, one must bear in mind the quality of the scientific study, i.e., the adequacy and appropriateness of the experimental design; the quality, competency, and completeness with which the study was carried out and reported; and the quality of the evaluation and interpretation of the test results. When addressing the caliber of the evaluation and interpretation of results from epidemiologic studies, the reliability of the data would be increased given the following factors:

- Are the arrived at results from well-designed and well-executed case–control and cohort studies that are free of bias?
- Do the results display a strong association, not likely due to chance variation?
- Do they follow a logical, temporal sequence of exposure response?
- Have they been replicated in a variety of settings?
- Do they exhibit a dose–response relationship?
- Are they toxicologically plausible?

Similarly, when looking at animal experimentation, are the results replicated in more than one experimental setting, species, strain, or, when appropriate, gender or sex? Do they exhibit a dose–response relationship? Are they based on a dosing regimen or route of exposure similar to that likely to be encountered by humans? Is the test animal employed in the experiment known to or likely to process (i.e., absorb, metabolize, excrete) the test chemical in the same or similar manner as humans.?

In many instances, we find situations where the results of a risk assessment may not be plausible based on what we know about the world. Dr. Houk is concerned about, for example, trichloroethylene and perchloroethylene, and the differences between the experimental and epidemiological data. One example that I came across was when I was working on vinyl chloride. Most of the 100 plus cases of vinyl chloride-induced angiosarcoma of the liver that were ever identified were in workers. To determine if there was the possibility of neighborhood cases, I collected all the cases that could be found in the whole country for an 11-year period to see whether these diagnosed individuals lived near the boundaries of chemical production facilities. Very few to almost none were found, but that was in the years 1964 to 1974. With a 50- or 60-year latency, and it may take that long for the neighborhood cases to occur, there still might be some occurences. If someone actually went to look for them, cases might be found. Because this is a very rare disease, it is actually possible to find the bulk of cases in the country. There have been risk assessments that look at vinyl chloride. They look at vinyl chloride-induced cases in the general population on a risk assessment basis and come up with calculations of 1 in 10,000 risk to people living near chemical production facilities. This is an issue that can be studied. I think it is important to the extent possible to actually apply real-world knowledge, epidemiologic studies, studies of humans, to these kinds of issues to try to answer them.

One of the risks of risk assessment is that the public has difficulty dealing with some of the numbers. They must be helped to understand the difference between upper bounds and estimates; they must understand the difference between lifetime risks and annual risks. I am not sure the general population understands that a one in a million risk applied to a group of 30 people has a different connotation than when applied to the entire country, and I think we have to live with these kinds of basic understandings. It is interesting to examine the things that relate to one in a million risk: 3/4 of a cigarette, 0.5 liter of wine, 0.5 minutes of rock climbing, 40 tablespoons of peanut butter, living for 1 day at age 12, many

years of living with dioxins in soil at some level that commonly occurs, and so on.

In conclusion, I would like to make some recommendations for research in the three areas of general toxicology, estimating and projecting risk, and epidemiology. First, I would suggest five proposals in the area of general toxicology: 1) enhance research on the interaction between toxic chemicals and genetically susceptible hosts; 2) enhance the development and improvement of *in vitro* and *in vivo* predictive toxicology systems; 3) enhance the development and improvement of biomarkers as early indices of exposure and as early diagnostic sentinels with specificity in predicting health outcomes of individuals; 4) encourage experimental research clarifying the relationship of animal variables such as weight and dietary composition on the molecular basis of toxicologic end points; and 5) encourage the development of interspecies comparison in toxicologic research to better understand and better predict qualitative and quantitative differences in the response to toxic chemicals.

Suggestions with regard to estimating and projecting risk include: 1) encourage the development and validation, when possible, of mechanistically based mathematical models particularly for noncancer health outcomes; 2) encourage the validation of the assumptions used in risk assessment approaches; and 3) encourage the development of exposure assessment and dose–response assessment aimed at dealing with the prediction of risk from human exposure to many chemicals by many media routes at varying levels.

Suggestions for epidemiology include: 1) encourage epidemiologic studies aimed at testing the accuracy of risk projections derived from animal data and modeling; 2) ensure that exposure and disease registries are established when they are scientifically justified and helpful in terms of epidemiologic studies; 3) encourage epidemiologic studies that incorporate biochemical and molecular probes to clarify exposures, precursor states, and mechanisms of actions; and 4) encourage epidemiologic studies that evaluate interactions between toxic chemicals, life styles, and host susceptibility.

We need to continue to use risk assessment. In the absence of more certain data, risk assessment is all we have, and just as it should not be denigrated as not helpful because of its inevitable limitations, neither should it be oversold as a panacea. We must apply risk assessment with the soundest professional and scientific judgment available in order to shape public policy that is scientifically defensible.

APPENDIX A
POSTER ABSTRACTS

1. ASSESSING RISK OF RELATED CHEMICALS: CURRENT REGULATORY PRACTICE AND ADDITIONAL OPTIONS

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Risk assessment of chemicals relies on an assessment of the toxic effects that may occur as well as the doses at which such effects may occur (i.e., the potency). Closely related chemicals are often assumed to have similar toxic effects but with differing potencies. If data were available for all endpoints for all chemicals within a family, decisions would be simple. In the absence of data, however, regulatory practice has differed. For example, different congeners of polychlorinated dibenzo-*p*-dioxins (PCDDs) are assigned different carcinogenic potencies based on results from a combination of cancer bioassays and short-term tests. Relying solely on short-term tests, the information on PCDDs has been extrapolated to polychlorinated dibenzofurans. In contrast, even though several mixtures of polychlorinated biphenyls (PCBs) have been examined in cancer bioassays with differing results, the Environmental Protection Agency (EPA) currently assumes all PCB mixtures are of equivalent potency. Although a third family of chemicals, the chlorinated ethenes, includes a human carcinogen (vinyl chloride), not all of the members of this family are treated as carcinogens by EPA (e.g., *trans*-1,2-dichloroethene). The implications for risk assessment of these divergent approaches to families of chemicals will be presented, along with consideration of alternatives for the relative potency of various mixtures of PCBs.

2. DEMOGRAPHIC CHARACTERISTICS AND CAREER EXPOSURE PROFILES OF ARMY SOLDIERS

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Army personnel have career assignments and individual job duties that follow certain predictable patterns. These assignments and job duties expose soldiers to hazardous chemicals that are clearly different than exposure profiles that exist in civilian industry. Soldiers remain in the working aspects of their military occupational specialty (MOS) for approximately 15 years before being promoted into positions with duties that are mainly administrative. Career assignment patterns during this 15-year period have been identified. Within each assignment, regular rotations between field exercises and garrison administrative, maintenance, and training periods occur. Differences between assignments are mainly associated with rank. Because these career assignment patterns are somewhat predictable, periods of potential exposure can be reliably estimated. Studies of exposures to chemicals in the field workplace can be extrapolated into these periods of potential exposure and used to derive career exposure estimates. Demographic profiles have also been developed that allow an examination of age, rank, time in service, sex, and race structure for each MOS. This type of information is useful for developing information on susceptible subpopulations which can be applied to risk estimates or military-unique standards. The U.S. Army Biochemical Research and Development Laboratory has developed preliminary career exposure profiles and demographics for Armored Vehicle Crewmen and Smoke Generator Operators to illustrate the nature of data available for these MOSs.

3. ECOLOGICAL RISK ASSESSMENT AT ABERDEEN PROVING GROUND, MARYLAND

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Potential ecological impacts associated with past chemical agent testing, munitions testing, and waste disposal are being evaluated for eight solid waste management units (SWMUs) at Aberdeen Proving Ground (APG) in Maryland. Aberdeen Proving Ground consists of approximately 80,000 acres of coastal plain uplands, wetlands, and estuary on the upper Chesapeake Bay. The site supports diverse terrestrial wildlife populations, including large breeding and over-wintering populations of the federally endangered bald eagle. In addition, the waters surrounding APG provide critical spawning and nursery habitat for approximately 40 of the 50 fish species that occur in the upper Bay as eggs or larvae. The primary focus of the ecological assessment is potential impacts to the fishery, although the potential impacts in terrestrial species also will be evaluated. Population-level impacts in selected aquatic species will be assessed using matrix-type population models and estimates of age-specific fecundity and mortality. Species to be evaluated will be selected based on considerations of life history and the spatial and temporal distribution of the various species relative to the SWMU locations. Toxicity data ranging from life-cycle tests to quantitative structure–activity relationships will be used in the assessment. The results of the risk assessment will be used to identify those areas where further study is needed.

4. ORDNANCE CHEMICAL DEGRADATION PRODUCTS: CONSEQUENCES OF EXCLUSION FROM RISK ASSESSMENTS

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For a variety of reasons, including resource and analytical limitations and availability of toxicity information, ordnance chemical degradation products often are not evaluated as part of remedial investigation studies. However, failure to include such chemicals in these studies contributes to uncertainties and may result in under-estimation of exposures and risk.

Degradation products and their parent compounds are compared with respect to their fate, transport characteristics, and toxicity. Solubility and half-life are used as crude measures of mobility and persistence. LD_{50} values are used as general measures of toxicity due to the paucity of chronic toxicity data for the less well studied breakdown products. Parent compounds and breakdown products that exhibit significantly different fate, transport, and toxicity characteristics are identified. Based on this information, the consequences of excluding degradation products from the risk assessment are discussed qualitatively. This information may be useful in designing remedial sampling plans that address degradation products that may contribute significantly to exposures and risk.

5. A RISK-BASED PROGRAM FOR SCREENING CONTAMINATION LEVELS AT HAZARDOUS WASTE SITES

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A computer program is presented which allows initial screening of contaminant levels at a hazardous waste site to decide when further, more detailed health risk analysis is required. Standard assumptions, recommended by the U.S. EPA for use in health risk assessments, are used to compute screening concentrations in air, soil, ground water, and surface water.

This program allows for prioritization of contaminant data at hazardous waste sites so that chemicals that require additional analyses for health risks can be separated from chemicals that do not require further study. The approach could be used to decide which analytical techniques are necessary (i.e., whether or not expensive, low-detection level methods are justified).

Screening concentrations are computed based on standard risk assessment relationships and assumptions, rather than detection above background. The program computes both short- and long-term exposures from all likely pathways for each contaminant and reports the lowest screening levels for any pathway. In addition, a safety factor is introduced in the program to account for the additive exposures from different pathways and contaminants. The default value of the safety factor is 100, which means that screening levels should result in exposures of less than one percent of accepted values. The safety factor is variable to account for site-specific conditions.

The calculation methods and assumptions built into the program are described, as well as uses and limitations of the approach. A sample case study is provided.

6. RISK ASSESSMENT OF MUNITIONS CHEMICALS TO DEVELOP DRINKING WATER HEALTH ADVISORIES

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The U.S. Army and the U.S. Environmental Protection Agency (EPA) established a Memorandum of Understanding to cooperate in developing Health Advisories (HA) on munitions chemicals that may occur in drinking water. Health Advisories, developed by the Office of Drinking Water, describe nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations. They provide informal technical guidance that assists public health officials when contaminations occur.

Health Advisories are developed for One-day, Ten-day, Longer-term (7 years or 10% lifetime) and Lifetime exposures based on noncarcinogenic toxicity. A threshold dose–response relationship is assumed.

Lifetime HAs are not recommended for known or probable human carcinogens. A potency value (unit risk) may be used to calculate risk for a lifetime exposure to carcinogens in drinking water. The unit risk usually is derived from the linearized multistage model with 95% upper confidence limits and provides an approximation of cancer risk that may exist. The value is only an estimate because cancer risk can vary by orders of magnitude when other models (e.g., the One-hit, Weibull, Logit and Probit models) are employed. Current understanding of carcinogenic mechanisms do not suggest that any one model can predict risk more accurately than another.

Published Lifetime HAs (micrograms per liter [µg/L]) include:
Nitroglycerin (5µg/L), Nitrocellulose (not toxic),
Trinitrotoluene (2 µg/L), RDX (2 µg/L), HMX (400 µg/L), and
Diisopropylmethyl phosphonate (600 µg/L).

7. A RISK-BASED METHOD FOR SETTING SOIL CLEANUP LEVELS AT HAZARDOUS WASTE SITES

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Cleanup of hazardous waste sites is often driven by remediation of contaminated soils. This is true both for protecting human health and the environment, as well as in terms of the total remedial cost. Soil remediation often accounts for a substantial portion of the total cleanup cost. It is vital that rational methods are used to evaluate alternatives for soil remediation to ensure adequate protection of public health while avoiding unnecessary costs.

This paper presents a method for evaluating the residual risk presented by chemicals left in soils at hazardous waste sites. The approach focuses on exposure to humans via domestic use of contaminated ground water. Although analytical equations are presented for each fate and transport component of the exposure pathway, the conceptual approach is amenable to the insertion of any specific fate and transport model, including sophisticated numerical studies of chemical transport.

A recent case study is discussed where the approach presented was used to back-calculate acceptable soil concentrations for 26 organic chemicals at a Superfund site in Pennsylvania. Although back-calculation is useful for setting initial cleanup goals, the method is unable to account for the specific performance of the remedial alternative chosen. Therefore, a forward assessment of residual site risks should be performed for evaluating the final attainment of cleanup objectives.

8. UNCERTAINTIES IN RISK ASSESSMENT: USES IN RISK MANAGEMENT AND RESEARCH PRIORITIES

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A graphical display of uncertainties in cancer risk assessment has been developed that shows various combinations of maximum individual risk and population risk (incidence) in terms of subjectively determined probabilities that they are nearest to being "true." Each estimate is derived by combining estimates of cancer potency, maximum exposure, average exposure, and number of people exposed.

A criterion band that shows combinations of maximum individual risk and population risk that are "acceptable" can be plotted on the same axes. Visual inspection then suggests whether the risk situation portrayed is reasonably judged to be "safe" (implying that no action needs to be taken), "unsafe" (meaning that controls should be imposed without further investigation), or "indeterminate" (meaning that further risk characterization is desirable before a risk management decision is finalized). The patterns also may be examined to decide which aspect(s) of the risk estimates contribute most to uncertainty in risk management and are therefore leading candidates for further research.

9. RISK ASSESSMENT USING STATISTICAL ESTIMATES OF KEY PROCESS AND POPULATION EXPOSURES IN THE SERVICE AREA OF AN AMERICAN ARMY MEDICAL CENTER IN THE FEDERAL REPUBLIC OF GERMANY

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Quantification of personnel exposures in a large group of military installations served by a U.S. Army medical center in West Germany was initiated following a preliminary survey of worksites by technician-level staff. Severe limitations on professional staff, necessitated development of an approach in which characteristic and "worst case" operations were evaluated initially. Data was pooled to estimate the exposure of specific processes and by inference the range of exposures of larger populations. Several critical processes and operations were identified as accounting for a high proportion (approximately 60%) of the chemical agent exposures. This data indicates the most severe exposures are to heavy metals generated in abrasive paint removal and welding operations. Deficiencies in available engineering control measures and protective equipment were common and tended to be similar throughout various workplaces. In this situation, a program-wide approach is strongly recommended to correct the occupational exposures based upon the group of worksites as a whole rather than on an individual basis.

10. UNCERTAINTY IN ESTIMATING EXPOSURES TO HAZARDOUS CHEMICALS FROM WASTEWATER TREATMENT LAGOONS FORMERLY USED FOR DISPOSAL OF HAZARDOUS WASTE

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The quality of a human health risk assessment is tied to the data on which it is based. Specific data needs for a quantitative risk assessment include: identification of the contaminants present at the site, accurate quantitative characterization of the nature and extent of contamination, identification of exposure points at which contact with the contaminants may occur, information regarding the frequency and magnitude of contact, the adverse health effects produced by each contaminant, and identification of the population(s) exposed. Current guidance available from the Environmental Protection Agency (EPA) assumes all these data will be available.

Risk assessments for the Department of Defense present special challenges because some of these needs may not be met to the extent required by EPA guidance. The authors recently completed a quantitative risk assessment in which the extent of contamination was not fully characterized for all environmental media known or reasonably suspected to be contaminated. A series of modeling steps was required to estimate the concentrations of contaminants in all media. The use of a series of models probably overestimated the extent of contamination. The resulting estimates of carcinogenic and noncarcinogenic risk were in excess of levels generally considered acceptable. Because the "true" extent of contamination is unknown, it is not possible to estimate the contribution of multiple modeling to the excess risk identified. The presentation will demonstrate how each successive modeling step introduced additional conservatism into the risk assessment; the impact of multiple modeling will be assessed qualitatively by examining the effects on different exposure routes.

11. INHALATION OF VOLATILE CHEMICALS FROM RESIDENTIAL USE OF CONTAMINATED WATER

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Indoor emissions may occur as a result of volatilization of chemicals indoors during use of contaminated water (e.g., while showering). Based on air-water partition coefficients and ventilation equations, it can be predicted that indoor use of water contaminated with volatile compounds will pose as great or greater health risk to residents as drinking 2 L/day (standard drinking water ingestion rate) of the same water. Indoor air sampling data supports the potential significance of inhalation exposure to contaminants in the water supply. Despite this potential, available guidance on how to quantify exposure to chemicals that volatilize from the water during home use is sketchy.

For the baseline risk assessment of a site involving contaminated ground water, the authors devised a methodology to quantify inhalation exposure while showering, operating a dishwasher, and operating a washing machine. The methodology involves assumptions and algorithms to estimate: (1) concentrations of chemicals in the breathing zone as a result of these activities; and (2) inhalation intake by potentially exposed individuals. Necessary assumptions included answering questions such as: what is the air exchange rate in a "typical" bathroom?; what is the water-flow rate from the "typical" shower?; how long is the cycle time of a "typical" dishwasher and washing machine?; and how much time does a person spend unloading the dishwasher and washing machine? A set of data used to answer these and other questions will be presented and the resulting contribution of inhalation exposures in the home will be discussed.

12. HEPATIC MODELS IN RISK ASSESSMENT

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By incorporating relevant physiological and biochemical parameters into different mathematical structures, different physiologically based pharmacokinetic, or PBPK models may lead to different predictions in risk assessment. In the search for accuracy and predictive power, PBPK models have developed in complexity from compartmental models to homogeneous capillary models (in which all capillaries are assumed functionally identical), to heterogeneous capillary models (in which there are statistical distributions of pharmacokinetically relevant properties such as capillary flows or enzyme contents).

In the liver, this progression is illustrated by the venous equilibration (v.e.) model, the undistributed sinusoidal perfusion (u.s.p.) model, and the distributed sinusoidal perfusion (d.s.p.) model. Although these models may fit specific data sets equally well (as measured for example, by least squares), they may predict quite different values for certain common pharmacokinetic parameters (such as the Michaelis constant Km). Because they are often used to extrapolate far beyond the ranges in which they are tested experimentally, the models may lead to quite different assessments of risk. It is therefore important to test the models by specific experiments designed to discriminate between them. For example, Keiding & Chiarantini, *J. Pharmacol. Exp. Ther.* 205, 465, 1978, refuted the v.e. model by flow change experiments in rat livers, whereas the u.s.p. model was refuted in favor of the d.s.p. model in pig livers by Bass & Robinson, *Microvasc. Res.* 22, 43, 1981. So far, the d.s.p. model has not been experimentally refuted, and remains the model of choice in risk assessment.

By using these models in conjunction with standard interspecies scaling techniques for hepatic blood flow and maximum elimination capacity Vmax, explicit expressions can be derived relating the (measured) extraction fraction for rat liver with the (predicted) extraction fraction for human liver according to all three models for both first-order elimination and general Michaelis-Menten kinetics. The v.e. and u.s.p. models retain their usefulness by providing upper and lower bounds on such extrapolations.

13. ON THE CHEMICAL RISK FROM NUCLEAR WASTE REPOSITORIES

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High, acute doses of radiation or high, acute intakes of chemical poisons can produce deleterious effects. For these cases, the risk for lethality can be used to compare chemical and radiological toxicities. Such comparisons are of a very limited value in the study of nuclear waste repositories because large, single intakes of contaminants are unlikely. A much more likely situation is the intake of very small quantities of contaminants involving either a radiological risk, or a chemical risk, or both types of risks. Apart from their radiotoxicity, the elements introduced in a nuclear waste repository may exhibit a certain chemical toxicity. Although, in the short term, the radiological toxicity of the materials in a nuclear waste repository is of primary concern, the potential chemical toxicity should not be overlooked. In the longer time frame (some hundred thousands of years), as radioactive decay depletes the radionuclides, the chemical toxicity may even become the dominant risk. The methodical tools applied for the radiation safety analysis of a repository for nuclear waste are also suitable for the chemical components. In this paper, the literature in the field is reviewed and some conclusions are drawn concerning the chemical risk of nuclear waste repositories.

14. PARAMETER SENSITIVITY IN PBPK MODELS OF METHYLENE CHLORIDE

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Application of physiologically based pharmacokinetic (PBPK) modeling to dose surrogate calculations and interspecies extrapolation provides a useful logical basis for quantitative risk assessment. However, these applications raise additional concerns as to the sensitivity of model outcome to the choice of model parameter values. This is of particular concern when trying to estimate the uncertainty in model extrapolations as a result of uncertainty in model parameter values. The fact that these models represent biological entities adds constraints to the estimation of parameter sensitivity. It is necessary to vary model parameters in a biologically realistic fashion in order to not introduce artifacts in the sensitivity analysis process.

We have examined the sensitivity of output variates to changes in model parameters of a methylene chloride PBPK model. Output variates for both parent compound and pathway dose metrics were examined. Results of these analyses will be presented as a function of species and parent compound dose.

15. RISK ASSESSMENT FOR THE NEW BRIGHTON/ARDEN HILLS SUPERFUND SITE

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PRC Environmental Management, Inc. (PRC) prepared a draft risk assessment report (RA) for the United States Environmental Protection Agency (EPA) assessing the risks to human health posed by the New Brighton/Arden Hills Superfund site in Ramsey County, Minnesota. The site is ranked No. 43 on the National Priorities List. It covers an area of approximately 25 square miles, which includes a 4-square mile area of the Twin Cities Army Ammunition Plant (TCAAP); and a 21-square mile off-TCAAP area contaminated by migration of contaminants from TCAAP. The groundwater and soils at the site are contaminated with volatile organic compounds (VOCs) and metals. Preparation of the RA and other ongoing remedial investigation/feasibility study (RI/FS) tasks are required under the Federal Facilities Agreement (FFA) between the U.S. Army (Army) and EPA; the Minnesota Pollution Control Agency (MPCA) is also a party to the agreement. This FFA was the first agreement in the country pursuant to Section 120 of the Superfund Amendment and Reauthorization Act (SARA).

A scoping meeting attended by EPA, MPCA, the Army, and their contractors was held to determine the overall nature and scope of the RA. Based on this meeting, the Draft RA was prepared utilizing EPA's Risk Assessment Guidance for Superfund, Human Health Evaluation, Part A (EPA 540/1-89-002) based primarily on data presented in RIs prepared for the Army (evaluating multimedia contamination on-TCAAP) and MPCA (evaluating groundwater contamination off-TCAAP). Risks were evaluated for exposure pathways involving exposures on-TCAAP and off-TCAAP, under two land use conditions: (1) the Army continues to operate TCAAP, with restricted access and (2) the Army abandons TCAAP and the land is developed as residential, commercial, and industrial property.

Exposures to groundwater and VOCs released from on-TCAAP remedial actions pose the greatest risks to human health. However, exposure to contaminated groundwater is largely speculative and is likely to be limited. Exposures to surface water and sediment pose little risk to human health. Risks from exposure to soils are difficult to assess and must be interpreted cautiously.

16. PREDICTING *IN VIVO* RATES OF METABOLISM OF VOLATILE ORGANIC CHEMICALS FROM *IN VITRO* KINETIC CONSTANTS: IMPLICATIONS FOR RISK ASSESSMENT

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Physiologically based pharmacokinetic (PBPK) models are being increasingly utilized to estimate target tissue doses of toxic chemicals and their metabolites in quantitative health risk assessments. A key component in these models are rates of chemical metabolism. Although it is most appropriate to obtain *in vivo* rates of metabolism for chemicals, this is not always possible in animals and is essentially impossible in humans, the species of interest. *In vitro* methods can be used to estimate *in vivo* kinetic constants but care must exercised to ensure that there is a good correlation between them and the *in vivo* situation. A 14-compound data set was used in this work to compare *in vivo* V_{max} values with *in vitro* constants. The data set included: benzene, toluene, *m*-xylene, styrene, chloroform, carbon tetrachloride, 1,1-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, 1,1,2,2-tetrachloroethane, 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene. *In vivo* constants were obtained by gas uptake and *in vitro* constants from enriched liver homogenate fractions. A regression of *in vivo* on *in vitro* V_{max} values (μ moles/h/rat) resulted in the equation: V_{max} (*in vivo*) = $2.26 \times V_{max}$ (*in vitro*) + 4.52 ($r^2 = 0.784$). Thus, this vial equilibration approach gave constants that correlated with *in vivo* values. At this stage of development however, it is important to identify which of the many available *in vitro* approaches correlate most consistently with *in vivo* behavior before *in vitro* rates from animal or human tissues can be used confidently in PBPK models.

17. RISK ASSESSMENT OF AIR CONTAMINANTS FROM OPEN BURNING/OPEN DETONATION AT THE UTAH TEST AND TRAINING RANGE: EVALUATING RISKS FROM ACUTE EXPOSURES

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A risk assessment was performed of the air emissions resulting from open burning/open detonation (OB/OD) of various types of explosives and propellants at the Utah Test and Training Range (UTTR) near Lakeside, Utah. The results of the risk assessment are being used to support a RCRA Part B Subpart X permit application.

Open burning/open detonation is performed at the UTTR on a sporadic basis in an isolated area, although large quantities of materials can be involved. Modeling indicated that people could be exposed to air pollutants for durations ranging from a few minutes to 1 h. Consequently, only acute exposures result. This is in contrast to the chronic exposure that is typically the subject of risk assessments.

Acute exposures require the development of different measures of toxicity than are normally employed in a risk assessment. National Ambient Air Quality Standards (NAAQS) were used when available. For other compounds, occupational ceiling or short-term exposure limits were used as toxicity measures during the indicator selection process. These occupational limits were used because they were available for most compounds predicted to be emitted and because they were derived for an exposure duration comparable to that which results during OB/OD. Compounds that only have 8-h occupational limits were excluded from consideration. For risk characterization purposes, values comparable to an acute reference dose had to be developed on an individual basis for compounds without NAAQS standards.

18. APPLICATION OF RISK ASSESSMENT TO DECISION MAKING AT HAZARDOUS WASTE SITES - SEEKING REAL NET RISK REDUCTIONS

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One key step in evaluating hazardous wastes sites is the development of a risk analysis that ties discovered chemical contamination with human and environmental health effects. These studies are Endangerment Assessments or Risk Assessments. Site contaminants are projected into possible future locations or concentrations in an effort to quantify current risks posed by a site, and future risks posed by a site should no action be taken to lessen the existing sources and concentrations. Subjective, highly conservative assumptions are often built into the process attempting to avoid underestimation of possible risks. Unfortunately, the assumptions often render the results meaningless in terms of usefully guiding decision making.

Presented here is a method used to perform a risk assessment such that regulatory demand for conservatism was met while retaining a useful site risk assessment for defining real risks and measuring possible risk reductions from remedial technologies. The method evaluated information drawn from a real site in two ways. First, chemical and site data were combined to determine actual site risks to human and environmental health. Second, conservative risk projections were used to emulate the basic regulatory endangerment assessment process. Following these separate analyses, remedial alternatives were presented with the likely obtainable reductions in contaminant concentrations following completion of remediation. Risks were recalculated with the newly remediated concentrations. Results show that one method obscures the actual net risk reduction while the other highlights it.

19. DESIGN-PHASE REVIEW OF HAZARDOUS MATERIALS IN AIR FORCE WEAPON SYSTEMS - A PROCEDURAL FRAMEWORK

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The Acquisition Management of Hazardous Materials (AMHM) Program was established by Air Force Systems Command to create an integrated oversight process for ensuring that consideration is given to hazardous materials issues during the weapon system acquisition process. The emphasis is on eliminating or reducing the use of hazardous materials in products and their associated processes during the entire life cycle of the weapon (manufacture, operation, maintenance, and disposal). The environmental and human health impacts of using a material should be examined in the design phase of the weapon so as to minimize unforeseen downstream costs and negative impacts on schedule and performance.

A crucial element of the AMHM program is the process by which hazardous substances are identified and evaluated. Although there already exist documented methods for evaluating hazardous materials which are used in government and industry, the Air Force needs a procedure specifically adapted to its needs. Such a procedure must take into consideration the specific context in which the material is to be used, relevant regulations, existing scientific data, and alternative materials and processes. A proposed procedural framework will be presented in terms of functional flow diagrams, organizational responsibilities, and informational requirements.

20. DERMAL EXPOSURE: DATA BASE, PREDICTIVE MODELS, AND RISK ASSESSMENT

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Prediction of the detrimental toxic effects of hazardous chemical exposure to the skin is difficult because of the complexity of the percutaneous absorption process and the lack of any consistently identifiable relationships between transport rate and chemical properties. The ultimate objectives of our research, therefore, are to address these problems and to be able to predict accurately the toxicokinetics of chemicals absorbed across human skin *in vivo*.

The methodological approach involves: (1) Establishing a data base of the extensive percutaneous absorption literature, and extracting relevant measurements of skin penetration. (2) Developing refined models of the percutaneous transport process that recognizes the relevant biology of the skin and the physicochemical interactions between the penetrating chemical and the skin. (3) Determining and validating practical relationships between the structure and physicochemical properties of the dermally contacting chemicals and the percutaneous transport kinetics. (4) Demonstrating how these "structure-activity" relationships can be used to reduce uncertainty in the risk assessment process.

The bibliographic data base now contains over 2500 records, and data abstraction into spreadsheet software has been performed for certain specific chemical classes (e.g., phenols), and for selected Environmental Protection Agency (EPA)-identified priority pollutants. Initial quantitative structure-activity relationships have been explored and families of curves, relating percutaneous permeability to penetrant lipophilicity and molecular volume, have been deduced.

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21. DEVELOPING EXPOSURE SCENARIOS FOR ASSESSING HUMAN HEALTH EFFECTS OF COMBUSTOR EMISSIONS

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Exposure scenarios are real or hypothetical situations that define the source and pathways by which individuals are exposed to environmental chemicals. Exposure scenarios are used in risk assessment of combustion facilities (e.g., municipal waste combustors) to evaluate the impact of emitted pollutants on human health and the environment. An approach to constructing site-specific exposure scenarios to aid exposure/risk assessors has been developed. In this approach, the source is defined in terms of its length of operation, and the exposed individual is defined in terms of his/her location, amount of time spent near the source, age, and lifestyle (e.g., urban or rural). The environmental media near the source (soil, water, vegetation) and the ways these media are used (drinking water, food, recreation) define the routes by which individuals are exposed. Average, moderate, and worst-case exposure scenarios have been developed to illustrate a range of possible situations. These scenarios, along with the advantages and disadvantages of using this approach for constructing exposure scenarios, will be presented.

22. DETERMINING HUMAN EXPOSURE TO POLLUTANTS MEASURED IN THE AMBIENT AIR EMITTED FROM A MUNICIPAL WASTE COMBUSTOR

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A pilot study of chemicals in ambient air surrounding a municipal waste combustor (MWC) was undertaken in an attempt to determine human exposure. Several metals (e.g., lead and nickel) and organics (e.g., benzo[*a*]pyrene, polychlorinated dibenzo-*p*-dioxins [PCDDs], and polychlorinated dibenzofurans [PCDFs]) were measured. The likelihood that the MWC was the source for these pollutants was evaluated using three approaches: (1) correlation of the amount of waste burned daily with particulate concentrations, (2) comparison of ambient air PCDD/PCDF congener profiles with those of potential sources (i.e., MWC stack emissions and residential wood burning systems), and (3) statistical analyses of the relationship between daily measured ambient air concentrations of pollutants and daily concentrations predicted form the Industrial Source Complex Short-Term air dispersion model. The daily measured concentrations were compared to the predicted concentrations by using two nonparametric procedures: a modified sign test and Friedman two-way analysis of variance. None of these analyses found a significant relationship between incinerator operation and measured pollutant concentrations. Advantages for each of these approaches of source apportionment are discussed.

23. A STATISTICAL TEST FOR EVALUATING COMPATIBILITY OF TWO OR MORE STUDIES IN CANCER RISK ASSESSMENT

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Frequently, there are two or more data sets available on which quantitative risk estimates for carcinogenicity could be based. Combining these data may in some cases result in improved estimates. A statistical method for evaluating the hypothesis that two or more sets of data are compatible with a common dose-response model would aid the biologist in making the determination whether to combine or not combine data sets. A statistical test based on the likelihood ratio principle is proposed for comparing two or more data sets to a common linearized multistage model. This test with several examples and the results of a Monte Carlo study of the power of the test are presented. The theoretical relationship between the proposed test and the methods commonly used to estimate parameters and confidence limits for the linearized multistage model are discussed.

24. BIOLOGICAL CONSIDERATIONS FOR COMBINING CARCINOGENIC QUANTITATIVE ESTIMATES

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Carcinogen risk assessments conducted by the United States Environmental Protection Agency have most frequently been based on results of a bioassay from a single sex/strain/species of animal. Use of more of the available data may result in a higher level of confidence in the risk estimate. Several biological factors should be considered before combining data sets from different animal sexes, strains, species, or tumor sites. The relevance of the animal models, study design and execution, dose selection, and route of administration are study quality factors which influence whether studies should be combined. The decision to combine data sets is also based on what is known of the mechanism of action of the agent (i.e., whether the agent is thought to be an initiator or to act at later stages, its pharmacokinetics, any species/sex specificity of the effect, and considerations regarding tumor site specificity). The use of these factors in the decision to combine or not combine data sets is discussed.

25. GENERAL GUIDANCE FOR ECOLOGICAL RISK ASSESSMENTS AT AIR FORCE INSTALLATIONS

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General guidance has been developed for performing ecological risk assessments (ERA) that not only conforms with Federal and Regional Environmental Protection Agency (EPA) regulations but also meets the special requirements of the Air Force Installation Restoration Program (IRP). It must be borne in mind that the geographic locations included in the ERA should not be limited by property boundaries if affected environments or habitats extend beyond them. An ERA can be completed in three phases.

Phase I (Ecological Quotients) is outlined by the following sequential steps.

1. Assemble all data relevant to the ERA. Identify all ecological contaminants (EC), locate sources of EC, estimate source size, and describe site history.
2. Establish background (ambient) concentrations of all EC.
3. Identify EC of concern using background concentrations site history, and potential for ecotoxicity.
4. Develop a physical model of the study area describing the likely migration pathways of EC (based on topography, hydrogeology, geology, geochemistry).
5. Identify ecological receptors, including endangered species, critical habitats, and sensitive environments. Be cognizant of seasonal variations in life cycle of target species. Determine recreational and commercial uses of the study area.
6. Conduct a field survey to verify information gathered to date.
7. Identify data gaps; gather additional required information, if necessary.
8. For each EC, establish assessment endpoints (e.g., toxic effects) and determine effective concentrations of EC in the target species. If data are not available, ecological benchmarks (e.g., EPA Ambient Water Quality Criteria) may be used as surrogates.
9. Characterize present and future completion of potential exposure pathways predicted by the physical site model and quantitate dose to receptors including ecological food chain considerations. Evaluate potential magnitude and frequency of contact with EC.
10. Develop an Ecological Risk Characterization for each EC and receptor of concern by comparing calculated exposure with effective concentration.
11. Consider the impacts of present or future human activities including any ongoing or proposed remediation that may affect the ecological resources at or near the study area.

Phase II (Biological Diversity) is analogous to human epidemiology studies and is used to bolster the findings of Phase I. The following steps are followed.

1. Define the boundaries of the territory to be studied and the period of time (season).
2. Identify a nearby, similar, but uncontaminated area.

3a. Perform a census of all extant species including total number of species (richness) and numbers of individuals for each species (evenness).

3b. Alternatively, monitor the distribution of selected species (i.e., a suite of species that is representative of the area and endangered, declining, and important species.

4. Compare the results of contaminated and control areas.

Phase III (Population Study) is performed if a decline in population size for an important species occurs with a low ecological quotient or no effect is seen with a high ecological quotient. A census of the number of individuals in each life stage for selected species is taken at several time points over one to several life cycles or seasons.

ERA is an ongoing process that should begin early in the IRP. The ERA should be modified and adjusted throughout the IRP as additional or more accurate data become available.

26. OCULAR EXPOSURE TO SOMAN: A SHORTCUT TO THE BRAIN?

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Exposure to soman gas has been linked to alterations in electroencephalograms and psychological disturbances, including inability to concentrate and failure to plan effectively. These cognitive activities take place in the forebrain structures of the anterior cerebrum. Anatomical considerations of the vascular supplies to the eye, orbit, and brain suggest that the ocular route of exposure may provide rapid, direct access of soman to the anterior portion of the brain so that exposure by this route may be of comparable importance to inhalation exposure.

Vapors or liquid droplets of soman contact both the cornea on the eyeball and the epithelium lining the inner side of the eyelid. Diffusion of soman can occur into either structure. Diffusion through the cornea provides access to the aqueous humor, a fluid that is constantly produced by the ciliary body posterior to the iris. The aqueous humor exits the eyeball into veins that coalesce and enter the skull, emptying into the large cavernous sinus (CS) located at the base of the brain. Soman that diffuses into the aqueous humor would follow this route. Soman can also diffuse into the conjunctiva (lining of the eyelid), a well-vascularized tissue, the venous drainage of which also joins the veins draining the eyeball proper, enters the skull, and finds its way to the CS.

The CS is important because several significant structures pass through it, bathing in the blood contained therein. These structures include the internal carotid arteries (ICA), the sympathetic carotid plexus of nerves, and several cranial nerves (III, IV, VI, V_2, and V_3). Because the flow of venous blood through the CS is sluggish, equilibration of agent between the venous blood of the CS and the arterial blood in the ICA, which are bathed by the venous blood, is facilitated. Soman that diffuses into the ICA will be distributed with the blood that flows primarily into the anterior cerebral artery, the major blood supply to the forebrain structures of the anterior cerebrum. This means that soman that is absorbed via the ocular route may enter the brain without traversing the heart, the lungs, or the liver. In addition, experimental animals, including dogs and cats, possess a special modification of the ICA which greatly increases the surface area available for the diffusion and further facilitates the exchange of soman between the venous blood and the blood in the ICA.

Because of the potential significance of the ocular route of exposure to soman gas and the differences among species in the anatomy relevant to this route, it is imperative that ocular exposure be considered in the pharmacokinetic modeling of soman exposure in experimental animals and in the extrapolation of laboratory results to the human condition.

27. THE HYDROXYLAMINE MOIETY OF DEVELOPMENTAL TOXICANTS CAUSES EARLY EMBRYONIC CELL DEATH

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Cellular debris, an indication of cell death, is apparent in limb buds of gestational day (gd) 12 rabbit embryos when examined by light microscopy at 4 h after either subcutaneous (sc) injection of a teratogenic dose of hydroxyurea (HU, 650 mg/kg) to pregnant rabbits or an intrauterine (iu) injection of HU (180 µg/site) to embryos. Several chemicals that are structurally related to HU are also teratogenic; all of them possess a terminal hydroxylamine moiety (-NHOH). To investigate whether the -NHOH moiety is responsible for the early cell death, a series of five structurally related, -NHOH bearing chemicals were administered at equimolar doses either by sc or iu injection on gd 12. Four hours later, embryos were harvested and prepared for light microscopy. The -NHOH-bearing chemicals included hydroxylamine HCl, *N*-methyl hydroxylamine HCl, HU, acetohydroxamic acid, and hydroxyurethane. Cell death was obvious in limb buds from treated embryos of all groups. A second series of chemicals, structurally similar to the hydroxylamine-bearing series, but possessing a terminal -NH_2 group, were tested at equimolar doses by an identical protocol. The chemicals in the -NH_2 series included NH_3 (as NH_4OH), methylamine, urea, acetamide, and urethane. None of the -NH_2 chemicals caused cell death in limb buds at 4 h demonstrating that, for the chemicals tested, the early episode of embryonic cell death is associated with the terminal -NHOH group.

Because antioxidants (e.g., propyl gallate, ethoxyquin, NDGA) and the hydroxyl free radical scavenger, D-mannitol, delay HU-induced early embryonic cell death, the -NHOH chemicals were coadministered with propyl gallate (PG at 634 mg/kg or 225 µg/site) to determine the effect on early cell death. In all cases, PG prevented/delayed the early episode of cell death when embryos were examined histologically at 4 h. These results suggest that the rapidly occurring embryonic cytotoxicity may involve a free radical mechanism that requires the presence of a terminal -NHOH for initiation.

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28. AUTOMATED DOSING AND WEIGHING SYSTEM WITH AUDIT-TRAILED DATA ACQUISITION AND MANAGEMENT: A GLP COMPLIANT SYSTEM

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The In-life Dosing System is used to dose animals on studies at the National Center for Toxicological Research (NCTR). This program was developed to meet stringent tracking requirements for Department of Defense studies using surety agents. The program enforces a study-specific protocol to set the experimental parameters and drive the menus for the study.

To start the program, the technician logs on the VAX 780 Computer and identifies the dosing team, the study, and the room and equipment that will be used, and then proceeds to calibrate the equipment. The technician then adds the container with the chemical agent and primes the Micrometic Systems Automatic Pipette. When ready to begin dosing, the technician barcodes the animal identification (ID) and cage ID using an Intermec 9510 Barcode Reader, and weighs the animal on a Mettler PE11 balance. The weight value is transmitted directly into the NCTR In-life Dosing program. The system uses the weight, along with dosing parameters taken from study-specific files, to calculate the correct dose for the animal. The calculated volume information is sent to a Micromedic Pipette which draws up the required dose. The technician selects the proper site of administration and presses a foot-pedal to dispense the dose. A time-stamped record of the dosing or any aberration to the dosing protocol (spills, regurgitation, blocked needles, etc.) is stored permanently as part of a comprehensive audit trail on the NCTR data base along with other data relating to the study. The program will not allow an animal that has already received a dose to be accidentally redosed and the system prompts for animals that should have been dosed but were not and requires a technician comment for each case that remains undosed.

This program reduces errors by minimizing operator data entry, relying instead upon parameters read from files and instruments. Automatic calculation and highly accurate dispensing of the dose further ensures reliability. Data integrity has been validated and is maintained through conformance to the Food and Drug Administration Good Laboratory Practice (GLP) standards for Automated Data Processing. This system is a cost-effective tool for dispensing and tracking the chemical agent and minimizes the time required for hand entry recordkeeping (especially in a GLP environment). Prior to introducing this system, daily labor requirement for dosing a 100 rat GLP and surety-compliant 90-day subchronic study was 12-h/day (three technicians for 4 h). Since this system has been in operation, the daily labor requirement has been lowered to 2 h/day (two technicians for 1 h). Equivalent results have been achieved during the past three 90-day subchronic studies with increased accuracy in dosing and record keeping and, based upon discussions with technicians, reduced stress and fatigue.

29. NEGATIVE DOMINANT LETHAL STUDY OF LEWISITE IN CD-RATS

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Lewisite (2-Chlorovinyldichloroarsine, Agent L) was investigated as part of the U.S. Army Toxicological Program on Chemical Agents. Twenty male CD-rats per dose group received by gavage 1500, 750, or 375 µg/kg Lewisite or vehicle control (1 mL sesame seed oil) daily for 5 days. Positive control males were given 1 mL sesame seed oil by gavage (Days 1 through 4) and on Day 5 they were given an ip injection of 100 mg/kg ethyl methanesulphonate, a positive control mutagen. Each male was mated to two virgin females (12 weeks of age) per week for the next 10 weeks. Females were sacrificed on Gestational Day 14. At necropsy, the corpora lutea were counted and the uteri and contents were examined. Implantation sites were categorized as live/dead fetuses or early/late resorptions. No significant differences in reproductive indices were seen between treatment groups and the control group except for the positive control. Males were sacrificed during Week 13 and necropsied. Sperm morphology/motility, testicular histopathic evaluation, and morphometric analysis of seminiferous tubule cross-sections showed no significant differences between treatment groups and the control group. (Supported by U.S. Army Medical Research and Development Command, APO#88PP8860)

30. A STUDY OF THE METABOLISM AND NEPHROTOXICITY OF SEVERAL ALKYL-SUBSTITUTED CYCLOHEXANES

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Male Fischer 344 rats were dosed by gavage with the following alkyl substituted cyclohexanes: methylcyclohexane, ethylcyclohexane, isopropylcyclohexane, and tertiary butylcyclohexane. The urinary metabolites of the cyclohexane derivatives were isolated and identified by gas chromatography (GC) and GC/mass spectrometry. The classic signs of hydrocarbon-induced nephropathy were pathologically determined with isopropylcyclohexane and tertiary butylcyclohexane producing the major renal damage.

31. HAZARD EVALUATION OF TABUN (AGENT GA) IN CELL AND ANIMAL MODELS

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The chemical agent Tabun ([GA]; phosphoramidocyanidic acid, dimethyl-, ethyl ester) is one of several organophosphorus compounds being evaluated under contract with the support of the U.S. Army Medical Research and Development Command. Apart from numerous LD_{50} animal studies, GA had not been subjected to a detailed toxicological evaluation. The following studies have been completed: Phase I assays (LEHR): Ames Salmonella, mouse lymphoma (ML), *in vitro* sister chromatid exchange (SCE), *in vivo* SCE, Unscheduled DNA synthesis (UDS); Phase II: delayed neuropathy in chickens (LEHR), teratology in rats and rabbits, and a 90-day subchronic in rats.

GA was a relatively weak, direct acting mutagen in the Ames, ML and *in vitro* SCE assays. Ames assay: the test was weakly positive for concentrations up to 200 µg/mL, but revertants only increased by 50% above background. ML: the response increased linearly with dose of GA, and was three-fold higher than background at the 100 µg/mL. *In vitro* SCE: induction of chromatid exchanges increased linearly with dose but was not twice the background. GA was not activated by a rat liver S9 preparation in the above assays. *In vivo* SCE: there was no significant induction with 700 µg/kg GA , and higher doses were lethal. UDS: induction decreased in the primary hepatocytes as if the agent were toxic. Cytotoxicity of GA in several of the assays suggested the cyano-group may be a site of toxicity separate from the phosphoramidate group. Evidence favoring this hypothesis was obtained by demonstrating that GA (like cyanide itself) inhibited the oxygen consumption of chick embryo hepatocytes.

Ninety-day delayed neuropathy studies in which hens were injected five times per week at 70 µg/kg of GA (the highest tolerated dose with atropine protection) did not result in organophosphorus-induced delayed neuropathy, according to biochemical, locomotor, and histopathological tests. Neuropathy target esterase was not inhibited with a single dose of 125 µg/kg of GA, approximately the LD_{50} level. GA was not grossly toxic when administered to rats for 13 weeks by ip injection at 20.1, 56.3, and 113 µg/kg. There was a reduction ($p<0.05$) in body weight gain in the high dose animals. The developmental toxicity of GA was determined in a Standard Segment II protocol in both female rats and rabbits exposed by sc injection during gestation. GA did not produce an increase in developmental toxicity at the following doses (rabbits: 56.25, 112.5, 317; rats: 75, 150, 300 µg/kg/day.)

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32. DERMAL TOXICITY USING LP1846 LIQUID GUN PROPELLANT ON MALE MINIATURE HANFORD SWINE

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LP1846 liquid gun propellant (60.8% hydroxylammonium nitrate, 19.2% triethanolammonium nitrate, 20.0% water) is under development by the U.S. Army as a possible substitute for current solid gun propellants. The limited data that are available on several liquid gun propellant formulations, as well as their major components, indicate that they are toxic in several species. The major effects are erythrocyte crenation, Heinz body formation, and methemoglobin production. This study was undertaken to determine the maximum tolerated dose (MTD) for future LP1846 studies. A total of 10 male Miniature Hanford Swine, in two groups, were assigned to this study. Eight were treated with LP1846 (2 to 15%, 1 to 12.5%, 1 to 10%, 1 to 7.5%, 1 to 5%, 1 to 3.5%, 1 to 1.9%) and two negative controls (15% surface area with distilled water). Blood samples for methemoglobin levels were collected on day of allocation, and on Day 1 at 0, 2, 4, and 8 h, and Days 2 through 15. Blood samples for hematology/clinical chemistry (complete hematology, BUN, total protein, creatinine, albumin and ASAT) were collected on the day of allocation, and on Day 1 at 0, 2, 4, and 8 h, and Days 2 through 5, 8 through 12, and Day 15. All surviving animals were euthanized on Day 15. Histopathology was performed on sections of skin exposed to the test and control articles (both representative samples and lesions occurring in these areas). An additional skin tissue sample was collected from a site that was no less than 5.0 cm away from the edge of the treatment area. The animals were observed twice daily except during Study Days 2 through 4 where clinical observations were made four times daily. Skin irritation was graded according to standard methods. Results indicate that the MTD was 15% skin surface area. Methemoglobin levels in those animals increased rapidly to peak nonfatal levels (20 to 23%) between 72- and 96-h postexposure. As the methemoglobin concentration increased, the number of circulating erythrocytes decreased while the number of reticulocytes and Heinz bodies increased indicating removal of toxic erythrocytes and early release of immature erythrocytes from hematopoietic tissues. Clinical chemistry data indicated no detectable detriment to either renal or hepatic function in any of the rangefinding animals. Evaluation of the cutaneous irritancy of LP1846 indicated that the agent is an irritant and it was scored in the moderate-to-severe category. Histological examination of exposed skin indicates that healing was progressing. The epithelium was intact in each specimen examined.

33. *IN VITRO* MODULATION OF INTERCELLULAR COMMUNICATION BY XENOBIOTICS: A COMPARATIVE ANALYSIS

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Intercellular communication mediated by gap junctions appears to be of central importance in normal cellular homeostasis, tissue growth, and development. Hence, chemicals which aberrantly down-modulate gap junction function can be considered potentially toxic.

In our continuing efforts to develop biomarkers of toxic chemical interactions, we have compared the modulation in intercellular communication by a variety of xenobiotic chemicals of environmental importance in selected human and rodent tissue-derived cell culture models. The data obtained so far clearly indicated that several of the toxic chemicals, which have been documented as tumor promoters, hepatotoxins, neurotoxins, and reproductive toxins have inhibited GJIC as determined by the techniques developed in our laboratory. Furthermore, we have noted a tissue and cell type specificity in the response elicited by these chemicals.

These observations reinforce our contention that inhibition of intercellular communication is a useful biomarker for identifying potential toxic chemicals, and that there are distinct tissue specific differences in the response evoked by various chemicals. The latter also suggests the need to assess inhibition of gap junction function in more than one *in vitro* model and to understand the basic biochemical mechanisms involved in the regulation of gap junctional communication in different *in vitro* systems. (supported by US Air-Force-OSR #89-0325 and NIEHS-Superfund #P-42ES04911)

34. COMPUTATIONAL METHODS FOR THE RAPID IDENTIFICATION AND PREDICTION OF SUSPECT TOXIGENS

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Many toxigens function through interactions with cellular receptors; these are examples of biological recognition processes. The chemical nature of the receptor is often not well understood; however, by computing and comparing the electrostatic potentials around molecules that show a range of tendencies to interact with a given receptor, it is frequently possible to identify features in the molecular potential that promote or oppose a molecule's interaction with the receptor. This permits subsequent predictions of the biological activities of other, related molecules. A particularly realistic and effective procedure is to compute the potential on the surface of the molecule, because this is most representative of what the receptor actually encounters. We define the surface as the 0.002 electrons/bohr^3 contour of the molecular electronic density; thus, it reflects features unique to the molecule, such as bonds and lone pairs. Surface electrostatic potentials have been computed at the ab initio SCF STO-5G level for halogenated dibenzo-*p*-dioxins, dibenzofurans, benzoflavones, anthraquinone, and polycyclic hydrocarbons. The results have been related to the biological activities of these systems, and provide a basis for identifying suspect toxigens in these classes of compounds.

35. STATISTICAL ANALYSIS OF FISH VENTILATORY RESPONSE DATA. AN ON-LINE DATA ANALYSIS COMPUTER SYSTEM AND ITS APPLICATION TO THE EVALUATION OF LABORATORY AND FIELD EXPERIMENTAL DATA ON BLUEGILLS

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Laboratory determinations of maximum acceptable toxicant concentration (MATC) levels for fish and other aquatic organisms are commonly based on lethal and sublethal toxic effects. It has been suggested in the aquatic toxicology literature that toxicant concentrations near the MATC will result in changes in fish ventilatory patterns that manifest themselves in a relatively short period of time, such as hours or days.

Van der Schalie (1980) has developed an on-line computerized system for monitoring the ventilatory patterns of fish. This system monitors up to 32 fish individually and continuously for four responses: ventilatory rate, depth of ventilation, gill purge ("cough") rate, and whole-body movement. The monitoring system, housed in a mobile trailer, is brought to the stream location that is to be monitored. Summary data on the four ventilatory responses, continuously monitored within each fish, are recorded at 15-min intervals.

The ability to monitor ventilatory responses on a real-time basis gives rise to the statistical problem of how to detect shifts from normal baseline ventilatory patterns on a real-time basis. This presentation discusses a statistical approach, based on statistical control chart methodology, that was developed to accomplish this objective and describes a series of computer programs that implement this methodology. Several of these programs are incorporated into the on-line monitoring system; they will detect shifts from baseline ventilatory patterns on a real-time basis. The statistical approach and the associated computer programs are illustrated with experimental data that were obtained with the on-line ventilatory response monitoring system.

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36. FLOW CYTOMETRIC ANALYSIS OF HEPATOCELLULAR CHANGES IN FISCHER 344 RATS UPON *IN VIVO* EXPOSURE TO PERFLUORODECANOIC ACID (PFDA)

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The carcinogenic potential of compounds that induce peroxisome proliferation has become an important area of risk assessment. Peroxisome proliferators represent a group of structurally diverse compounds whose mechanisms of carcinogenesis remain to be fully determined. Perfluorodecanoic acid (PFDA), a perfluorinated carboxylic acid, is a halogenated hydrocarbon compound that induces hepatocellular peroxisome proliferation which can be evaluated by flow cytometric analysis. Hepatocytes were isolated from PFDA-treated, pair-fed control, and naive control Fischer 344 rats and analyzed for changes in cell size, granularity, and DNA content. The results indicate that PFDA increases both hepatocellular size and granularity, which correlates with reported light and electron microscopic changes. Perfluorodecanoic acid induces a shift in the normal predominant tetraploid DNA content to a diploid hepatocyte DNA population. This shift in DNA content may represent an early stage in the initiation of hepatocellular carcinogenesis.

This work was supported by Grant No. 88-0216 from the Air Force Office of Scientific Research.

37. EVALUATION OF HISTOPATHOLOGIC CHANGES AND MITOGEN-INDUCED PROLIFERATIVE RESPONSE OF LYMPHOID TISSUES ISOLATED FROM PERFLUORODECANOIC ACID (PFDA)-TREATED FISCHER 344 RATS

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An essential part of risk assessment is an evaluation of the immunotoxicologic changes associated with chemical exposure. The immune system is a highly sensitive indicator of potential chemical toxicity in both humans and animals. A complete immunotoxicologic evaluation of xenobiotics involves both humoral and cell-mediated immunity. Immunotoxicologic risk assessment should involve a tier-testing strategy such that initial investigative evidence may or may not point to further immunologic evaluation. Perfluorodecanoic acid (PFDA) is a perfluorinated carboxylic acid compound that exhibits toxic effects similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, a potent immunotoxicant. Experiments were designed to examine morphologic changes of various lymphoid tissues derived from Fischer 344 rats exposed to PFDA *in vivo*. Rats exposed to 50 mg/kg PFDA showed marked lymphoid depletion of the thymus (thymic atrophy). In addition, we also investigated mitogen-induced lymphocyte proliferation as one aspect of cell-mediated immune response.

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38. STRUCTURE-ACTIVITY MODEL OF MOUSE INHALATION LC_{50}

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A structure-activity model of mouse inhalation LC_{50} values has been developed. This model can be used for the estimation of mouse inhalation LC_{50} values from chemical structure. In addition to an equation capable of predicting values for heterogenous data sets, an equation was developed specifically for fluorohydrocarbons.

The 321 LC_{50} values were mostly collected from the open literature. Independent parameters consisted of MOLSTAC(c) substructural keys, molecular connectivity and kappa environment topological indices, and sigma and pi electronic charges. The equations were developed with multivariate regression techniques. Extensive diagnostic procedures were employed to assure the robustness of the equations.

In the most general model, 50% of the LC50 values are predicted within a factor of approximately 2.0, and two-thirds within a factor of 2.5. Ninety percent of the values are predicted within a factor of 5.

This model has been incorporated into the TOPKAT program to permit its convenient use by researchers and industrial health and regulatory personnel.

39. THE EFFECT OF TRICHLOROETHYLENE IN IRRIGATION WATER ON PLANT GROWTH

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Trichloroethylene (TCE) contamination of soil and/or groundwater is a problem at several Air Force installations. At one installation, TCE-contaminated water is used for the irrigation of nearby orchards. Concern has arisen as to the possible deleterious effect of TCE on the plants, and, by extension, to humans consuming these piants.

Bioassays utilizing germinated sorghum (*Sorghum bicolor* L.) and pinto bean (*Phaseolus vulgaris* L.) were performed. Multiple replications were exposed to several levels of TCE in water for 14-day periods. The plants were then harvested and mean shoot length and dry weight were compared among TCE concentrations. The concentrations of TCE and its metabolites in exposed and nonexposed plant tissue was also determined. The results obtained should be helpful in the development of biologically meaningful standards for groundwater contaminants.

40. A CASE STUDY OF A CATASTROPHIC TOXIC EXPLOSION – SOME INSIGHTS FOR AN EFFECTIVE EMERGENCY RESPONSE SYSTEM

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Castastrophic events such as rocket booster explosions, chemical plant fires/explosions, and nuclear plant disasters can release very large quantities of toxic substances into the environment over very short periods of time. Depending on the location and environmental conditions, these materials can spread extremely rapidly and place humans at risk. Such events pose a difficult challenge for an emergency response system (ERS) to deal with. This paper describes one such event – the explosion of a large rocket booster at Vandenberg AFB – and shows several implications this event has for effective ERSs that must deal with the atmospheric dispersion of toxic contaminants.

Predicting the probable path of the spreading toxic cloud as accurately and as rapidly as possible is the first function an ERS must perform. This requires knowledge of atmospheric conditions and suitable models for describing the transport and dispersion of the toxic material. Too often, however, models are employed that have not been adequately tested against the conditions for which they are being used, or the meteorological data used for input to the models are not timely or of adequate spatial resolution. Also, the models may not be initialized with good data on characteristics of the source term (e.g., height and width of the stabilized toxic cloud). This paper illustrates the necessity for providing toxic dispersion models with timely data and shows examples of several sources of such data. Finally, examples are shown on how essential data could be displayed in real-time as part of an ERS.

41. EVALUATION OF OTTO FUEL II FOR TERATOGENIC EFFECTS PHASE TWO: NONRODENT SPECIES

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OTTO Fuel II is the propellant used in the Navy's MK 46 and MK 48 torpedoes. Navy personnel guidelines authorize the assignment of female crew members to billets involving the fueling and maintenance of these torpedoes. These policies have raised questions regarding the potential for OTTO Fuel II to cause birth defects.

Studies were initiated in early 1988 to determine if OTTO Fuel II was teratogenic in the rat and rabbit. Results of the rat study revealed evidence of fetal toxicity only at doses which also caused significant toxicity to the dam. A reduction in maternal body weight during the dosing period was accompanied, in this study, by a reduction in fetal length and weight. An increase in the number of fetal resorptions and a decreased number of live fetuses was also noted. Because of a lack of significant gross morphologic malformations in any of the fetuses examined and the absence of toxic effects in fetuses from dams which did not themselves display toxicity, it was concluded that OTTO Fuel II was not a teratogen in the rat.

The present study replicates our previous work in a nonrodent species. Forty-eight artificially inseminated rabbits were dosed dermally with OTTO Fuel II at the rate of 0, 100, 316 and 1000 mg/kg/day on Days 6 through 18 of pregnancy. A significant reduction in maternal body weight was seen on Day 15 of pregnancy and occurred only in the high dose group. Liver weights recorded at necropsy were significantly elevated in this group. Morphologic examination of the rabbit fetuses failed to reveal significant evidence of fetal malformations or toxicity. A statistically significant reduction in the total number of live fetuses was noted, however, but only in those dams receiving the 1000 mg/kg/day dose. The preimplantation loss indicated that fetal death occurred very early in the developmental process in these animals. This fetal loss is possibly related to an increased level of blood methemoglobin in the dam. Based on data from both the rat and rabbit studies, we conclude that OTTO Fuel II is not a teratogen according to current Environmental Protection Agency testing guidelines.

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